Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Weinreich DM, Sivapalasingam S, Norton T, et al. REGEN-COV antibody combination and outcomes in outpatients with Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2108163

R10933-10987-COV-2067

This supplement contains the following items:

Clinical Study Protocol

A MASTER PROTOCOL ASSESSING THE SAFETY, TOLERABILITY, AND EFFICACY OF ANTI-SPIKE (S) SARS-COV-2 MONOCLONAL ANTIBODIES FOR THE TREATMENT OF AMBULATORY PATIENTS WITH COVID-19

Compound:	REGN10933+REGN10987, REGN10989
Clinical Phase:	1/2/3
Protocol Number:	R10933-10987-COV-2067
Protocol Version:	Original
Date of Issue:	*See appended electronic signature page*
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[redacted]

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACE2	Angiotensin-converting enzyme 2
ADA	Anti-drug antibody
ADE	Antibody-dependent enhancement
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
C_{max}	Maximum concentration
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
EC_{50}	Effective concentration of 50% viral neutralization
EC_{99}	Effective concentration of 99% viral neutralization
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
EUA	Emergency Use Authorization
FAS	Full analysis set
FDA	Food and Drug Administration
FIH	First-in-human
GCP	Good clinical practice
GLP	Good laboratory practice
IRB	Institutional Review Board
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IDMC	Independent data monitoring committee
INR	International normalized ratio
IRT	Interactive response technology
IRWS	Interactive web response system
IV	Intravenous
IVIG	Intravenous immunoglobulin

LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MERS-CoV	Middle East respiratory syndrome coronavirus
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NLR	Neutrophil-lymphocyte ratio
PK	Pharmacokinetic
PT	Prothrombin time
RBD	Receptor binding domain
Regeneron	Regeneron Pharmaceuticals, Inc.
REGN10933+REGN10987	Co-administered REGN10933+REGN10987 combination therapy
REGN10989	REGN10989 monotherapy
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis system
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
WHO	World Health Organization
WOCBP	Women of childbearing potential

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Master Protocol Assessing the Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Patients with COVID-19
Site Locations	The study will be conducted in up to approximately 100 sites in the United States.
Principal Investigator	To be determined

Objectives

Primary

Phase 1

Part A

- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- To evaluate the virologic efficacy of REGN10933+REGN10987 compared to placebo in reducing viral shedding of SARS-CoV-2

Part B

- To evaluate the safety and tolerability of REGN10989 compared to placebo
- To evaluate the virologic efficacy of REGN10989 compared to placebo in reducing viral shedding of SARS-CoV-2

Phase 2

To evaluate the virologic efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo in reducing viral shedding of SARS-CoV-2.

Phase 3

To evaluate the clinical efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo.

Secondary

Phase 1

Part A

- To evaluate additional indicators of virologic efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo
- To characterize the pharmacokinetic (PK) profiles of REGN10933 and REGN10987 in serum
- To assess the immunogenicity of REGN10933 and REGN10987

Part B

- To evaluate additional indicators of virologic efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the clinical efficacy of REGN10989 compared to placebo
- To characterize the PK profile of REGN10989 in serum
- To assess the immunogenicity of REGN10989

Phase 2

- To evaluate additional indicators of virologic efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the clinical efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo
- To evaluate the safety and tolerability of REGN10933+REGN10987 and REGN10989 compared to placebo

To characterize the concentrations of REGN10933, REGN10987, and REGN10989 in serum

- To assess the immunogenicity of REGN10933, REGN10987, and REGN10989

Phase 3

- To evaluate the virologic efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo in reducing viral shedding of SARS-CoV-2
- To evaluate the safety and tolerability of REGN10933+REGN10987 and REGN10989 compared to placebo
- To characterize the concentrations of REGN10933, REGN10987, and REGN10989 in serum
- To assess the immunogenicity of REGN10933, REGN10987, and REGN10989

Study Design

This is an adaptive, phase 1/2/3, randomized, double-blinded, placebo-controlled master protocol to evaluate the efficacy, safety, and tolerability of REGN10933+REGN10987 combination therapy and REGN10989 monotherapy in adult outpatients (ie, ambulatory patients) with COVID-19.

To be eligible, adult patients must have laboratory-confirmed SARS-CoV-2 and COVID-19 symptoms but must not have been previously hospitalized or currently hospitalized.

Sentinel Safety Group

Phase 1 will include a sentinel safety group, where the initial safety data through day 3 will be reviewed by an independent data monitoring committee (IDMC).

Patients in this sentinel safety group can be derived from either of 2 concurrent first-in-human (FIH) phase 1 studies (R10933-10987-COV-2067 in ambulatory patients, and R10933-10987-COV-2066 in hospitalized patients), where the safety and tolerability of REGN10933+REGN10987 (in part A) and REGN10989 (in part B) will be evaluated.

- Part A review: Patients will be pooled together from the phase 1 part A portions of either of the 2 studies. Once safety data have been collected through day 3 for a total of approximately 30 patients (from one or both of the studies combined), the IDMC will review the data.
- Part B review: Patients will be pooled together from the phase 1 part B portions of either of the 2 studies. Once safety data have been collected through day 3 for a total of approximately 20 patients (from one or both of the studies combined), the IDMC will review the data.

Phase 1 enrollment will pause during the IDMC review. Initiation of phase 2 enrollment is contingent upon IDMC review of phase 1 data from the sentinel safety group. Once phase 2 is active, phase 1 will continue to enroll to completion, but phase 2 enrollment will not require the completion of phase 1 enrollment.

Phase 1

In phase 1 part A, randomization will be limited to REGN10933+REGN10987 low dose, REGN10933+REGN10987 high dose, and placebo. In part B, randomization will be limited to REGN10989 and placebo Part B will begin enrollment only after the FDA completes review of the IND application for REGN10989 and notifies the Sponsor that patients may be dosed with REGN10989 (eg, the Agency informs the Sponsor that it is safe to proceed).

On day 1, eligible patients in part A will be randomized to a single intravenous (IV) administration of REGN10933+REGN10987 (low dose), REGN10933+REGN10987 (high dose), REGN10989, or placebo.

Patients will then be sequestered for the first 48 hours after dosing, during which time they will be closely monitored for serious adverse events (SAEs) and adverse events of special interest (AESIs). On day 3, patients can return home, if medically appropriate, after completing the day's assessments. After completing assessments on day 7, all patients will be sent home, if medically appropriate.

Throughout the study, safety information (SAEs and AESIs) will be collected, as will information about any medically-attended visits related to COVID-19. Nasopharyngeal (NP swab), nasal swab, and saliva samples will be collected to assess viral shedding.

	The study will end on day 29, when patients will have final assessments conducted in person including NP swab, nasal swab, and/or saliva sample collection (as feasible) and blood draws for PK, anti-drug antibody (ADA), and exploratory analyses. **Phase 2** On day 1, eligible patients will be randomized 1:1:1:1 to a single dose of REGN10933+REGN10987 (low dose), REGN10933+REGN10987 (high dose), REGN10989, or placebo. After infusion of study drug, patients will be observed for 2 hours and, if no SAEs or AESIs are observed, will be sent home. Nasal swab and saliva samples will be collected every other day for the first 2 weeks and then twice weekly thereafter. Information regarding SAEs, AESIs, and medically-attended related to COVID-19 will be recorded throughout the study. On day 29, patients will have final assessments conducted in clinic, including nasal swab and saliva sample collection and blood draws for PK, ADA, and exploratory analysis.
Study Duration	The duration of the study is 30 days for each patient.
End of Study Definition	The end of study is defined as the date when the last living patient completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).
Population	
Sample Size	Phase 1 will continue to enroll until up to 100 patients are randomized. Phase 2 will continue to enroll until up to 250 patients are randomized. It is estimated that 704 patients (176 patients per arm) will be required for phase 3.
Target Population	This study will enroll adult, non-hospitalized patients who have a positive RT-PCR test for SARS-CoV-2 and recent COVID-19 symptoms. A patient must meet the following key criteria to be eligible for inclusion in the study. Other inclusion criteria apply: • Has laboratory-confirmed SARS-CoV-2 infection (positive RT-PCR test) ≤72 hours of randomization • Is experiencing ≥1 of the following symptoms at randomization: fever, cough, shortness of breath • Has experienced COVID-19 symptoms for <7 days A patient who meets any of the following key criteria will be excluded from the study. Other exclusion criteria apply: • Has been admitted to a hospital prior to randomization, or is hospitalized (inpatient) at randomization, due to COVID-19 • Has participated, or is participating, in a clinical research study evaluating COVID-19 convalescent plasma, monoclonal antibodies against SARS-CoV-2, or intravenous immunoglobulin (IVIG) within 3 months or less than 5 half-lives of the investigational product (whichever is longer) prior to the screening visit • Has a history of COVID-19 investigational or Emergency Use Authorization (EUA)-approved treatments in the past 30 days or less than 5 half-lives of the investigational product (whichever is longer) prior to the screening visit. This includes, but is not limited to: remdesivir, hydroxychloroquine, tocilizumab, sarilumab, and other immunomodulatory agents • Current use of any COVID-19 investigational or EUA-approved treatment
Treatments	
Study Drug	• Co-administered REGN10933+REGN10987 combination therapy, 2.4 g (1.2 g each of REGN10933 and REGN10987) IV single dose

- Co-administered REGN10933+REGN10987 combination therapy, 8.0 g (4.0 g each of REGN10933 and REGN10987) IV single dose
- REGN10989 monotherapy, 1.2 g IV single dose

Placebo
- Placebo IV single dose

Endpoints

Primary

Phase 1

Part A and B

- Proportion of patients with treatment-emergent SAEs through day 29
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29
- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by quantitative reverse transcription quantitative polymerase chain reaction (RT-qPCR) in NP swab samples.

Phase 2

Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in saliva samples.

Phase 3

Proportion of patients with ≥1 COVID-19 related medically-attended visit through day 29.

Secondary

Phase 1

Virologic

- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in saliva samples
- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in nasal swab samples
- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples (NP swabs, saliva, or nasal swabs)
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in NP swabs
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in saliva samples
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in nasal swabs

Clinical

- Proportion of patients with ≥1 COVID-19 related medically-attended visit through day 29
- Proportion of patients with ≥2 COVID-19 related medically-attended visits through day 29
- Total number of COVID-19 related medically-attended visits through day 29
- Proportion of patients admitted to a hospital due to COVID-19 by day 29
- Proportion of patients admitted to an intensive care unit (ICU) due to COVID-19 by day 29
- Proportion of patients with ≥1 outpatient or telemedicine visit due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29

PK/ADA

- Concentrations of REGN10933, REGN10987, and REGN10989 in serum and corresponding PK parameters

- Immunogenicity as measured by ADA to REGN10933, REGN10987, and REGN10989 over time

Phase 2

Virologic

- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in nasal swab samples
- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples (saliva or nasal swabs)
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in saliva samples
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in nasal swabs

Clinical

- Proportion of patients with ≥1 COVID-19 related medically-attended visit through day 29
- Proportion of patients with ≥2 COVID-19 related medically-attended visits through day 29
- Total number of COVID-19 related medically-attended visits through day 29
- Proportion of patients admitted to a hospital due to COVID-19 by day 29
- Proportion of patients admitted to an intensive care unit (ICU) due to COVID-19 by day 29
- Proportion of patients with ≥1 outpatient or telemedicine visit due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29
- Days of hospitalization due to COVID-19
- Proportion of patients with all-cause mortality by day 29
- Proportion of patients with treatment-emergent SAEs through day 29
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29

PK/ADA

- Concentrations of REGN10933, REGN10987, and REGN10989 in serum
- Immunogenicity as measured by ADA to REGN10933, REGN10987, and REGN10989 over time

Phase 3

Virologic

- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in saliva or nasal swab samples
- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples (saliva or nasal swabs)
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in saliva samples
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in nasal swabs

Clinical

- Proportion of patients with ≥1 COVID-19 related medically-attended visit through day 29
- Proportion of patients with ≥2 COVID-19 related medically-attended visits through day 29
- Total number of COVID-19 related medically-attended visits through day 29
- Proportion of patients with ≥1 outpatient or telemedicine visit due to COVID-19 by day 29
- Proportion of patients admitted to a hospital due to COVID-19 by day 29

- Proportion of patients admitted to an intensive care unit (ICU) due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29
- Days of hospitalization due to COVID-19
- Proportion of patients with all-cause mortality by day 29
- Proportion of patients with treatment-emergent SAEs through day 29
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29

PK/ADA

- Concentrations of REGN10933, REGN10987, and REGN10989 in serum
- Immunogenicity as measured by ADA to REGN10933, REGN10987, and REGN10989 over time

Procedures and Assessments

Procedures and assessments will include the following:

Efficacy

- NP, saliva, and/or nasal swabs for SARS-CoV-2 RT-qPCR
- Medically-Attended COVID-19 Visit Details

Safety

- Serious adverse events and adverse events of special interest

Statistical Plan

Statistical Hypothesis

The primary statistical hypotheses for the primary efficacy endpoints for the phase 1 and phase 2 portion of the study are as follows:

- There is no treatment difference between REGN10933+REGN10987 2.4 g IV and placebo in terms of time weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22 versus there is a treatment difference
- There is no treatment difference between REGN10933+REGN10987 8.0 g IV and placebo in terms of time weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22 versus there is a treatment difference
- There is no treatment difference between REGN10989 1.2 g IV and placebo in terms of time weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22 versus there is a treatment difference.

The safety and tolerability objectives of phase 1 will be evaluated by estimating the proportion of patients with treatment-emergent SAEs through day 29 and hypersensitivity reactions (grade ≥2) including infusion-related reactions through day 29.

Justification of Sample Size

The sample size for phase 2 is based on the primary virologic endpoint of time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, using a two-sample t-test at a two-sided significance of α=0.05.

Assuming a standard deviation of 2.1 log_{10} copies/mL, a sample size of 20 patients per arm in phase 1 will have at least 80% power to detect a difference of 1.91 log_{10} copies/mL. The smallest treatment difference that will result in $p<0.05$ is approximately 1.34 log_{10} copies/mL.

Assuming a 10% dropout rate and standard deviation of 2.1 log_{10} copies/mL, a sample size of 50 patients per arm in phase 2 will have at least 80% power to detect a difference of 1.25 log_{10} copies/mL. If a standard deviation of 3.8 log_{10} copies/mL is assumed, the detectable difference would be 2.27 log_{10} copies/mL. A total sample size of up to 250 patients are needed including 150 patients randomized to placebo and the 2 REGN10933+REGN10987 combination therapies when phase 2 starts, and up to 100 patients randomized concurrently to placebo and REGN10989 monotherapy when it is available.

The initial estimate of the sample size for phase 3 is based on the phase 3 primary endpoint of proportion of patients with ≥1 COVID-19 related medically-attended visit. Assuming a

	10% dropout rate and 30% rate of patients with ≥1 COVID-19 related medically-attended visit in the control arm, a sample size of 704 patients (176 patients per arm) will have at least 90% power to detect a 50% reduction of the control rate (to 15%) in the treatment arm.
Statistical Analysis	**Primary Efficacy Analysis** The primary efficacy variable for phase 1 and phase 2 is time-weighted average change from baseline in viral shedding from day 1 to day 22. The estimand for the primary hypothesis is the difference in means between each of the anti-S SARS-CoV-2 mAb treatments and placebo in the primary efficacy variable in the FAS. The primary efficacy variable will be calculated using trapezoidal rule based on observed data and is analyzed using an Analysis of Covariance (ANCOVA) model with treatment group and randomization strata as fixed effects and baseline viral shedding as covariate. The least squares means estimates for the time-weighted average mean change from baseline in viral shedding for each treatment group, as well as the difference between each anti-spike mAb treatment arm and placebo, will be presented along with the corresponding p-value, standard error, and associated 95% confidence interval. The phase 3 primary efficacy variable is the proportion of patients with medically attended visits due to worsening COVID-19 symptoms and signs and will be compared between groups using stratified Cochran-Mantel-Haenszel test at two-sided 0.05 level. P-values and 95% confidence intervals for the treatment difference will be presented. **Safety Analysis** Safety data including serious adverse events and adverse events of special interest, vital signs, and laboratory tests will be listed and summarized by treatment group.

1. INTRODUCTION

1.1. Emergence of SARS-CoV-2 and COVID-19

Coronaviruses are a family of enveloped, single-stranded RNA viruses. In recent decades, two highly pathogenic strains of coronavirus were identified in humans: severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). These viruses were found to cause severe, and sometimes fatal, respiratory illness (Cui, 2019) (Fehr, 2015).

In December 2019, pneumonia of unknown cause was identified in clusters of patients in Wuhan City, China. A novel enveloped RNA betacoronavirus – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – was identified in these patients, and the disease caused by SARS-CoV-2 infection was later designated coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO, 2020b) (Zhu, 2020). As of May 2020, more than 5.5 million confirmed cases of COVID-19 have been reported globally (WHO, 2020a). The rapidly-spreading, worldwide outbreak has prompted the WHO to declare COVID-19 a pandemic and public health emergency of international concern.

1.2. Clinical Outcomes in Hospitalized Patients with COVID-19

Patients with COVID-19 are at risk for developing a variety of respiratory conditions, ranging from relatively mild symptoms to respiratory failure and death (Wu, 2020b). Among hospitalized patients, intensive care and/or supplemental oxygen intervention (eg, mechanical ventilation) is often required, and reported fatality rates are high.

In a report from the Chinese Center for Disease Control and Prevention that included 44,500 confirmed infections, nearly 20% of patients presented with advanced respiratory symptoms (14% with dyspnea, hypoxia, and >50% lung involvement on imaging; 5% with respiratory failure, shock, or multiorgan failure) (Wu, 2020b). Another analysis of patients with COVID-19 in China found that, among 1,099 hospitalized patients, 5% had been admitted to an intensive care unit (ICU), 2.3% required invasive mechanical ventilation, and 1.4% died. Among patients with advanced disease on admission (defined as pneumonia, hypoxemia, and tachypnea), these negative outcomes rose to 19%, 14.5%, and 8.1%, respectively (Guan, 2020). A report of 2634 hospitalized patients with COVID-19 in the United States identified similar clinical outcomes: 14.2% were admitted to an ICU, 12.2% required invasive mechanical ventilation, and 21% died (Richardson, 2020). Other reports have found that approximately 20% to 30% of hospitalized patients with COVID-19 and pneumonia require intensive care for respiratory support(Chen, 2020b) (Huang, 2020)

1.3. Outpatient Care as a Potential COVID-19 Treatment Setting

In contrast to hospital cases, published data for COVID-19 cases seen at emergency departments, urgent care centers, outpatient care or non-hospitalized settings are relatively limited. However, guidance has been provided by the Centers for Disease Control and Prevention (CDC) and other organizations for managing ambulatory patients and monitoring them for respiratory or other complications, indicating that some outpatient diagnoses may require subsequent hospitalization (CDC, 2020a). An anti-viral therapeutic that could be administered to ambulatory

(non-hospitalized) patients with COVID-19 has the potential to significantly reduce COVID-19 hospitalization and ICU admissions. Currently, there is a great need for therapies capable of reducing SARS-CoV-2 viral shedding and slowing or preventing COVID-19 disease progression.

1.4. The Role of Spike (S) Protein in SARS-Cov-2 Pathogenesis

Coronaviruses consist of an RNA genome packaged in nucleocapsid (N) protein surrounded by an outer envelope. The envelope is comprised of membrane (M) protein and envelope (E) protein, which are involved in virus assembly, and spike (S) protein, which mediates entry into host cells. S proteins form large trimeric projections, providing the hallmark crown-like appearance of coronaviruses. S protein trimers bind to a host receptor and, after priming by cellular proteases, mediate host–virus membrane fusion (Li, 2016). The S protein appears to be central to viral infectivity by SARS-CoV-2. SARS-CoV-2 S protein binds the host receptor angiotensin-converting enzyme 2 (ACE2) with high affinity, and in cell assays and animal models can utilize ACE2 as a functional receptor for host cell entry (Hoffmann, 2020) (Ou, 2020) (Walls, 2020).

Blockade of host cell entry through the use of neutralizing antibodies against of S protein is a viable mechanistic strategy shown to reduce viral infectivity of SARS-CoV and MERS-CoV (Jiang, 2020). In light of the likely pivotal role of S protein in the pathogenesis of SARS-CoV-2, a number of efforts are underway to develop antibodies and vaccines that target the S protein of this novel coronavirus.

1.5. REGN10933+REGN10987 and REGN10989: Fully Human Monoclonal Antibodies that Target SARS-CoV-2 S Protein

Regeneron Pharmaceuticals, Inc (Regeneron) is currently developing fully human, neutralizing mAbs directed against the S protein of SARS-CoV-2, for the treatment and prevention of SARS-CoV-2 infection. REGN10933, REGN10987, and REGN10989 are fully human, IgG1 monoclonal antibodies (mAbs) that bind the receptor binding domain (RBD) of the SARS-CoV-2 S protein and block interaction with ACE2. REGN10933 and REGN10987 exhibit potent neutralization and can bind simultaneously to the S protein RBD. When co-administered as combination therapy, REGN10933+REGN10987 treatment is anticipated to neutralize SARS-CoV-2 with a reduced likelihood of viral escape due to genetic mutations. REGN10989 exhibits exceptionally potent neutralization, suggesting potential use in a monotherapy setting. Importantly, all three mAbs retain neutralization potency against multiple SARS-CoV-2 S protein variants identified through clinical isolates. REGN10933+REGN10987 combination therapy and REGN10989 monotherapy thus represent promising therapeutic strategies to reduce SARS-CoV-2 viral shedding and COVID-19 disease progression.

1.6. A Randomized Study of Anti-SARS-CoV-2 S Protein Monoclonal Antibodies in Ambulatory Patients with COVID-19

Several therapeutic agents have been previously studied in the context of other coronaviruses (SARS-CoV and MERS-CoV), including corticosteroids, type 1 interferons, convalescent plasma, ribavirin, lopinavir/ritonavir, proteases, and agents targeting viral entry proteins, with generally inconsistent findings of efficacy (Sanders, 2020). Many of these therapies, as well as a number of novel treatments and vaccines, are under investigation for the treatment of COVID-19. Currently,

however, there is no approved treatment for use in ambulatory patients with COVID-19, and additional controlled trials are needed.

This is an adaptive, phase 1/2/3, randomized, double-blinded, placebo-controlled master protocol to evaluate the efficacy and safety of co-administered REGN10933+REGN10987 combination therapy ("REGN10933+REGN10987") and REGN10989 monotherapy ("REGN10989") in adult outpatients (ie, ambulatory patients) with COVID-19.

For more information regarding the rationale for the study design and dose selection, refer to Section 3.2. Additional background information on the study drugs and the overall development program can be found in the Investigator's Brochures.

2. STUDY OBJECTIVES

2.1. Primary Objectives

Phase 1

The primary objectives of phase 1 are:

Part A

- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- To evaluate the virologic efficacy of REGN10933+REGN10987 compared to placebo in reducing viral shedding of SARS-CoV-2

Part B

- To evaluate the safety and tolerability of REGN10989 compared to placebo
- To evaluate the virologic efficacy of REGN10989 compared to placebo in reducing viral shedding of SARS-CoV-2

Phase 2

The primary objective of phase 2 is to evaluate the virologic efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo in reducing viral shedding of SARS-CoV-2.

Phase 3

The primary objective of phase 3 is to evaluate the clinical efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo.

2.2. Secondary Objectives

Phase 1

The secondary objectives of phase 1 are:

Part A

- To evaluate additional indicators of virologic efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo
- To characterize the PK profiles of REGN10933 and REGN10987 in serum
- To assess the immunogenicity of REGN10933 and REGN10987

Part B

- To evaluate additional indicators of virologic efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the clinical efficacy of REGN10989 compared to placebo
- To characterize the PK profile of REGN10989 in serum

- To assess the immunogenicity of REGN10989

Phase 2

The secondary objectives of phase 2 are:

- To evaluate additional indicators of virologic efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the clinical efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo
- To evaluate the safety and tolerability of REGN10933+REGN10987 and REGN10989 compared to placebo
- To characterize the concentrations of REGN10933, REGN10987, and REGN10989 in serum
- To assess the immunogenicity of REGN10933, REGN10987, and REGN10989

Phase 3

The secondary objectives of phase 3 are:

- To evaluate the virologic efficacy of REGN10933+REGN10987 and REGN10989 compared to placebo in reducing viral shedding of SARS-CoV-2
- To evaluate the safety and tolerability of REGN10933+REGN10987 and REGN10989 compared to placebo
- To characterize the concentrations of REGN10933, REGN10987, and REGN10989 in serum
- To assess the immunogenicity of REGN10933, REGN10987, and REGN10989

2.3. Exploratory Objectives

The exploratory objectives in all phases of the study are:

- To evaluate the development of treatment resistance to REGN10933+REGN10987 and/or REGN10989
- To evaluate the impact on self-reported symptoms of REGN10933+REGN10987 and/or REGN10989 compared to placebo
- To explore the potential association of baseline humoral immune activity to SARS-CoV-2 on response to REGN10933+REGN10987 and/or REGN10989
- To evaluate the effects of REGN10933+REGN10987 and/or REGN10989 as compared to placebo on generation of a humoral immune response to SARS-CoV-2 (as measured by anti-SARS-CoV-2 N protein)
- To investigate the development of SARS-CoV-2 genetic variants resistant to REGN10933+REGN10987 and/or REGN10989

- To explore the effects of REGN10933+REGN10987 and/or REGN10989 on SARS-CoV-2 in vitro infectivity compared to placebo (as determined by viral culture)
- To explore biomarkers predictive of REGN10933+REGN10987 and/or REGN10989 safety, efficacy, and/or disease progression and COVID-19 clinical outcomes
- To understand the underlying mechanisms of action and biology of REGN10933+REGN10987 and/or REGN10989, SARS-CoV-2, and COVID-19
- To explore relationships between REGN10933+REGN10987 and/or REGN10989 exposure and selected efficacy and safety endpoints and/or biomarkers

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

Phase 1

Treatment of ambulatory patients with COVID-19 with REGN10933+REGN10987 and/or REGN10989 will be tolerated and will reduce viral shedding.

Phase 2

Treatment of outpatients with COVID-19 with REGN10933+REGN10987 and/or with REGN10989 will reduce viral RNA shedding.

Phase 3

Treatment of outpatients with COVID-19 with REGN10933+REGN10987 and/or with REGN10989 will improve clinical outcomes.

Information concerning statistical hypotheses can be found in Section 11.1.

3.2. Rationale

3.2.1. Rationale for Study Design

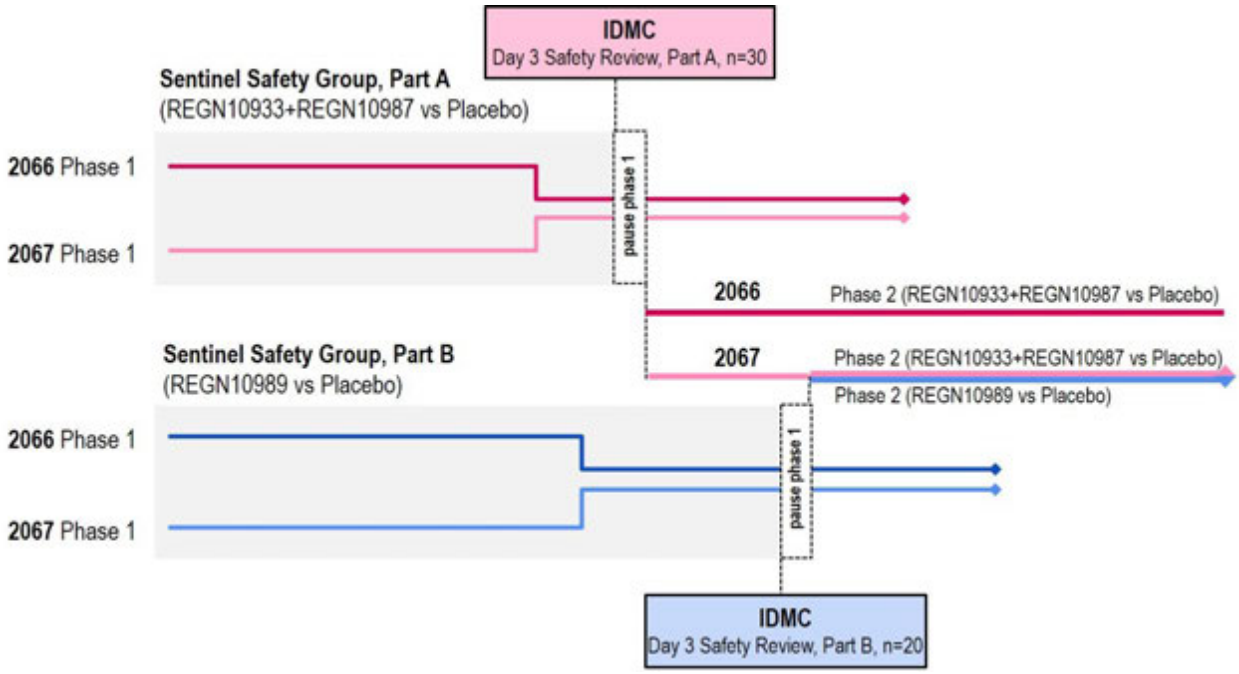
This randomized, double-blinded, placebo-controlled, adaptive phase 1/2/3 master protocol will assess the safety, tolerability, and efficacy of REGN10933+REGN10987 in hospitalized patients with COVID-19. The safety and tolerability of REGN10989 will also be evaluated in the phase 1 portion of the study to enable investigation of REGN10989 in other clinical settings. The multicenter conduct of this study will enable generalizable evidence of the safety, tolerability, and efficacy of these investigational mAbs for COVID-19.

3.2.1.1. Phase 1 Sentinel Safety Group

This master protocol will include a first-in-human (FIH) phase 1 study to evaluate safety and tolerability. Driven by the medical urgency of the COVID-19 pandemic, the process described below is designed to maximize efficient enrollment of eligible patients while optimizing safety of FIH exposure with limited preclinical data (see Section 3.3).

Phase 1 will include a sentinel safety group (Figure 1), where the initial safety data up to day 3 will be reviewed by an independent data monitoring committee (IDMC).

Figure 1: Phase 1 Sentinel Safety Group



Patients in this sentinel safety group can be derived from either of 2 concurrent FIH studies, where the safety and tolerability of REGN10933+REGN10987 (in part A) and REGN10989 (in part B) will be evaluated:

- R10933-10987-COV-2066, in hospitalized adult patients with COVID-19
- R10933-10987-COV-2067, in ambulatory adult patients with COVID-19

Two separate IDMC reviews will occur: one to assess REGN10933+REGN10987 (part A), and one to assess REGN10989 (part B).

- **Part A review:** Patients will be pooled together from the phase 1 part A portions of either of the 2 studies. Once safety data have been collected on day 3 for approximately 30 patients (from one or both of the studies combined), the IDMC will review the data.
- **Part B review:** Patients will be pooled together from the phase 1 part B portions of either of the 2 studies. Once safety data have been collected on day 3 for approximately 20 patients (from one or both of the studies combined), the IDMC will review the data.

Note that phase 1 enrollment will pause during the IDMC review.

Initiation of phase 2 enrollment is contingent upon IDMC review of phase 1 data from the sentinel safety group. After IDMC reviews and provides a positive recommendation for phase 1 part A, enrollment of studies assessing REGN10933+REGN10987 (including REGN10933+REGN10987 treatment arms in phase 2 of this study and R10933-10987-COV-2066) may begin. After IDMC reviews and provides a positive recommendation for phase 1 part B, enrollment of studies assessing REGN10989 (including the REGN10989 treatment arm in this study) may begin.

Once phase 2 of this study is active, phase 1 will continue to enroll to completion. However, phase 2 enrollment does not require the completion of phase 1 enrollment.

3.2.1.2. Adaptive Master Protocol Design

The study utilizes an adaptive master protocol design. The adaptive design has been selected to maximize the efficiency of identifying early signs of efficacy, increase the efficiency of studying multiple therapeutic combinations, and avoid the use of ineffective dose levels in patients with COVID-19.

Due to the novel nature of the COVID-19 pandemic, efficacy endpoints are not well established, and the standard-of-care is expected to evolve over time. The adaptive design of this study allows for the assessment of virologic and clinical efficacy endpoints in phase 2, which are then seamlessly confirmed in the phase 3 portion of the study, as well as evaluating the benefit risk of the different treatment arms.

This master protocol will allow for treatment arm(s) to be dropped if there is a clinically meaningful imbalance between treatment arms in the incidence of SAEs or the incidence of AESIs, or if there is a meaningful imbalance between treatment arms regarding efficacy endpoints.

The design will allow for the addition of new treatment arms with other anti-SARS-CoV-2 S protein mAbs as they become available for clinical testing (umbrella design), refinement of disease characteristics of eligible study populations (basket design), as well as other multiple adaptations, including dropping of a treatment arm, determination of phase 3 primary endpoints, and phase 3 sample size estimation.

3.2.1.3. Rationale for Primary Objectives

Safety and Tolerability

The primary objective of phase 1 is safety and tolerability, evaluated by targeted collection of treatment-emergent serious adverse events (SAEs) throughout the study and adverse events of special interest (AESIs) through day 29.

Many patients who are ambulatory and experiencing relatively early stages of COVID-19 may nevertheless present with complicated disease presentation at baseline or could quickly and unexpectedly deteriorate and progress to have a complicated disease presentation. As such, their treatment-emergent adverse event (TEAE) profile could be complex and dynamic. Accurately collecting such a large volume of TEAEs could impose unnecessary burden on an already over-strained healthcare system and frequent exposure to infected patients could increase the risk of infection to the study staff.

As such, evaluating targeted treatment-emergent SAEs and AESIs (≥grade 2 hypersensitivity reactions including infusion-related reactions) will provide the most relevant safety information to adequately evaluate the safety and tolerability of REGN10933+REGN10987 and/or REGN10989. This subset of treatment-emergent SAEs and AESIs encompasses the key safety concern that would be expected for mAbs targeting an exogenous target (see Section 3.3) and help evaluate unexpected serious adverse events.

Virologic Efficacy

The primary mechanism of action of REGN10933+REGN10987 and REGN10989 is blockade of the S protein RBD interaction with ACE2, leading to decreased infectivity of host cells. Blocking viral entry would result in reductions in SARS-CoV-2 RNA replication, and corresponding viral

shedding in affected tissues. In phase 1 and phase 2, the primary virologic endpoint will therefore evaluate, as proof of mechanism, the ability of REGN10933+REGN10987 and REGN10989 to reduce viral shedding in the upper respiratory tract. Day 22 (21 days after dosing) was chosen as the cutoff date for this analysis, based on accumulating evidence that this time period approaches the lower limit of detection in samples collected from the upper respiratory tract in patients spontaneously recovering from COVID-19 (He, 2020) (Cao, 2020) (Wang, 2020c).

Clinical Efficacy

Clinical efficacy will also be evaluated. Patients will be enrolled in this study at or near their initial diagnosis of COVID-19 and are therefore expected to have comparatively mild or less advanced disease. By directly targeting host entry by SARS-CoV-2, REGN10933+REGN10987 REGN10989 may impact the early stages of the disease course, mitigating early disease progression and reducing the likelihood that patients will experience the more advanced symptoms associated with hospitalization and/or other urgent medical visits. The study will therefore assess the proportion of patients requiring COVID-19 related medically-attended visits (defined in Section 9.3.3.2) subsequent to their initial disease diagnosis and release to home quarantine.

3.2.1.4. Stratification According to Risk of Hospitalization Due to COVID-19

In phase 2 and phase 3, randomization will be stratified based on risk factors for hospitalization due to COVID-19 (refer to Section 8.6 for complete definition of risks factors).

Although more advanced COVID-19 illness can occur in individuals of all ages, it primarily occurs in older adults or those with underlying medical conditions, including cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease, obesity (body mass index [BMI] >30), cancer, and chronic kidney disease (CDC, 2020b) (Lighter, 2020) (Wu, 2020b) (Zhou, 2020).

Hospitalization rates for COVID-19 increase with age, with one study reporting a 1% hospitalization rate for those 20 to 29 years, 4% rate for those 50 to 59 years, and 18% for those >80 years of age (Liu, 2020). Moreover, the majority of those hospitalized or in ICUs are older adults. Among 4,226 COVID-19 cases reported in the United States during February and March 2020, for example, 45% of hospitalizations and 53% of ICU admissions for COVID-19 were among adults ≥65 years of age (CDC, 2020c).

In addition to older patients, younger patients with underlying medical conditions may be at higher risk for hospitalization due to COVID-19. Among 7,162 patients reported in the United States with COVID-19 who had data available on their underlying health conditions, for example, patients with underlying conditions were hospitalized at higher rates compared to those without underlying conditions (27.3% to 29.8% compared to 7.2% to 7.8%). The most common underlying conditions in the study were diabetes mellitus, cardiovascular disease and chronic lung disease (CDC, 2020b).

Obesity is prevalent condition that may also be a risk factor for hospitalization with COVID-19, with one study reporting that young obese patients (BMI >30) were more likely to be hospitalized or admitted to an ICU compared to young patients who were not obese (Lighter, 2020). In the United States, nearly 40% of adults are obese and may be at higher risk of hospitalization due to COVID-19 (CDC, 2017).

3.2.2. Rationale for Dose Selection

This study will assess a single IV dose of REGN10933+REGN10987 as combination therapy in a 1:1 ratio as well as IV administration of REGN10989 as a single agent. The 1:1 ratio for REGN10933+REGN10987 is thought to be appropriate as these are non-competing mAbs targeting non-overlapping epitopes of the RBD of the S protein of SARS-CoV-2, with similar in vitro binding and neutralization properties (for more information, refer to the Investigator's Brochure[s]). The study will evaluate the co-administered REGN10933+REGN10987 as combination therapy at an initial dose level of 2.4 g (1.2 g per mAb), which is expected to be an efficacious dose (see below). The study will also evaluate REGN10933+REGN10987 at a higher dose, 8.0 g (4.0 g per mAb), in the event that a higher dose is required for efficacy.

The study will also assess single dose, intravenous REGN10989, a mAb that has at least 5-fold greater in vitro neutralization potency (EC50) than either REGN10933 or REGN10987. Based on this difference in potency, REGN10989 will be tested at 1.2 g; a dose equivalent to the initial dose level for each of the individual mAbs in the combination therapy REGN10933+REGN10987. Although the primary goal is to assess safety and tolerability of REGN10989 in this study, the use of a lower dose will allow a greater ability to discriminate the potential superior activity of this antibody as monotherapy for use in other studies. REGN10989 will not be further assessed in this protocol after Phase 1.

Cellular entry of coronaviruses depends on binding of the S protein to a specific cellular receptor and subsequent S protein priming by cellular proteases. ACE2 is the receptor for cellular entry of SARS-CoV-2 and its gene expression has been reported in the lungs, particularly in type-2 alveolar epithelial cells and bronchial airway epithelium (Wu, 2020a) (Xu, 2020) (Zhao, 2020). The strategy taken for dose selection in this study was to identify a target concentration in lung epithelial lining fluid (ELF) that approximates the effective concentration of 99% viral neutralization (EC99) observed against live virus in vitro and to then identify a dose that will meet or exceed this concentration in lung ELF. The effective concentration for 99% of neutralization (EC99) against live virus is 0.14 µg/mL (REGN10933), 0.80 µg/mL (REGN10987), and 0.01 µg/mL (REGN10989).

An average lung ELF-to-serum mean Cmax ratio of ~0.15 has been reported for other exogenous IgG1 mAbs for the treatment of Staphylococcus aureus lung infections (Magyarics, 2019). It is assumed that the lung ELF-to-serum Cmax ratio is 0.15 for REGN10933, REGN10987, and REGN10989. Dividing the target lung ELF concentration by this ratio, the associated serum concentration for these targets is therefore estimated to be ~at least 5 µg/mL for the combination of REGN10987+REGN10933, and ~0.1 µg/mL for REGN10989.

Taking into account uncertainties regarding mAb penetration into lung ELF, prediction of human PK, and effects of disease on PK, 20 µg/mL was selected as a target concentration in serum for the initial dose of REGN10933+REGN10987 combination therapy. The goal for the initial REGN10933+REGN10987 combination dose is for ≥95% of patients to exceed the target serum concentration for 28 days after dosing. Based on healthy subject human PK data for six Regeneron mAbs directed against an exogenous target (N=6 to 12 subjects per mAb), a single IV combination dose of 1.2 g per mAb is predicted to result in ≥95% of patients exceeding the target serum concentration for 28 days after dosing.

A 4-week Good Laboratory Practice (GLP) toxicology study in cynomolgus monkeys is currently ongoing and assessing once-weekly dosing of up to REGN10933+REGN10987 (at 150 mg/kg per antibody) and REGN10989 (150 mg/kg) is being conducted to support safety of these mAbs.

3.3. Risk-Benefit

An assessment of risks and benefits is provided in the Investigator's Brochure(s).

4. ENDPOINTS

4.1. Primary Endpoint

Phase 1

The primary endpoints for phase 1 are:

Part A and B

- Proportion of patients with treatment-emergent serious adverse events (SAEs) through day 29
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29
- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by quantitative reverse transcription quantitative polymerase chain reaction (RT-qPCR) in nasopharyngeal (NP) swab samples.

  Note: Time-weighted average of change from baseline viral shedding from day 1 to day 22 will be calculated for each patient using the trapezoidal rule as the area under the curve for change from baseline at each time point divided by the time interval for the observation period.

Phase 2

The primary endpoint for phase 2 is time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in saliva samples.

Phase 3

The primary endpoint for phase 3 is proportion of patients with ≥1 COVID-19 related medically-attended visit through day 29.

4.2. Secondary Endpoints

Phase 1

Virologic

- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in saliva samples
- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in nasal swab samples
- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples (NP swabs, saliva, or nasal swabs)
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in NP swabs
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in saliva samples

- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in nasal swabs

Clinical

- Proportion of patients with ≥1 COVID-19 related medically-attended visit through day 29

  Note: COVID-19 related medically-attended visits are defined in Section 9.3.3.2.
- Proportion of patients with ≥2 COVID-19 related medically-attended visits through day 29
- Total number of COVID-19 related medically-attended visits through day 29
- Proportion of patients admitted to a hospital due to COVID-19 by day 29
- Proportion of patients admitted to an intensive care unit (ICU) due to COVID-19 by day 29
- Proportion of patients with ≥1 outpatient or telemedicine visit due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29

PK/ADA

- Concentrations of REGN10933, REGN10987, and REGN10989 in serum and corresponding PK parameters
- Immunogenicity as measured by anti-drug antibodies (ADA) to REGN10933, REGN10987, and REGN10989 over time

Phase 2

The secondary endpoints for phase 2 are:

Virologic

- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in nasal swab samples
- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples (saliva or nasal swabs)
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in saliva samples
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in nasal swabs

Clinical

- Proportion of patients with ≥1 COVID-19 related medically-attended visit through day 29

- Proportion of patients with ≥2 COVID-19 related medically-attended visits through day 29
- Total number of COVID-19 related medically-attended visits through day 29
- Proportion of patients admitted to a hospital due to COVID-19 by day 29
- Proportion of patients admitted to an ICU due to COVID-19 by day 29
- Proportion of patients with ≥1 outpatient or telemedicine visit due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29
- Days of hospitalization due to COVID-19
- Proportion of patients with all-cause mortality by day 29
- Proportion of patients with treatment-emergent SAEs through day 29
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29

PK/ADA

- Concentrations of REGN10933, REGN10987, and REGN10989 in serum
- Immunogenicity as measured by anti-drug antibodies (ADA) to REGN10933, REGN10987, and REGN10989 over time

Phase 3

The secondary endpoints for phase 3 are:

Virologic

- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in saliva or nasal swab samples
- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples (saliva or nasal swabs)
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in saliva samples
- Change from baseline in SARS-CoV-2 viral shedding at each visit through day 29, as measured by RT-qPCR in nasal swabs

Clinical

- Proportion of patients with ≥1 COVID-19 related medically-attended visit through day 29
- Proportion of patients with ≥2 COVID-19 related medically-attended visits through day 29
- Total number of COVID-19 related medically-attended visits through day 29

- Proportion of patients with ≥1 outpatient or telemedicine visit due to COVID-19 by day 29
- Proportion of patients admitted to a hospital due to COVID-19 by day 29
- Proportion of patients admitted to an ICU due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29
- Days of hospitalization due to COVID-19
- Proportion of patients with all-cause mortality by day 29
- Proportion of patients with treatment-emergent SAEs through day 29
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29

PK/ADA

- Concentrations of REGN10933, REGN10987, and REGN10989 in serum
- Immunogenicity as measured by anti-drug antibodies to REGN10933, REGN10987, and REGN10989 over time

4.3. Exploratory Endpoints

The exploratory endpoints for phase 1 and phase 2 are:

- Development of resistance to SARS-CoV-2 in NP, saliva, or nasal samples through day 29
- Change and percentage change in neutrophil-lymphocyte ratio (NLR) at each visit through day 29
- Change and percentage change in D-dimer at each visit through day 29
- Change and percentage change in ferritin at each visit through day 29
- Change and percentage change in C-reactive protein (CRP) at each visit through day 29
- Change and percentage change in lactate dehydrogenase (LDH) at each visit through day 29
- Change in SE-C19 item scores over time
- Change in PGIS score over time
- PGIC score at day 29

5. STUDY VARIABLES

This section provides variables to be measured in the study. For description and rationale of corresponding study procedures, refer to Section 9.3.

5.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, etc), disease characteristics, medical history, and medication history for each patient.

5.2. Efficacy Variables

Efficacy variables include viral shedding (log_{10} copies/mL), number of COVID-19 related medically-attended visits, number of patients admitted to a hospital, ICU, or outpatient telemedicine visit, and number of patients requiring mechanical ventilation.

5.3. Safety Variables

Safety variables include incidence of treatment-emergent SAEs and incidence of AESIs Section 10.1.3.

5.4. Pharmacokinetic Variables

For phase 1, the PK variables are the concentration of REGN10933, REGN10987, and REGN10989 in serum at each time point, and select PK parameters. For phase 2, the PK variables are the concentration of REGN10933, REGN10987, and REGN10989 in serum at each time point The PK sampling time points are specified in the schedule of events (Table 1 and Table 2).

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, and time-point/visit. Samples will be collected at the visits specified in the schedule of events (Table 1 and Table 2).

5.6. Pharmacodynamic and Other Biomarker Variables

Exploratory endpoint variables may include, but not be limited to, parameters reported in complete blood counts with differential, levels of D-dimer, ferritin, CRP, LDH, per-symptom SE-C19 score, PGIS score and PGIC score.

These results may be reported outside of the clinical study report (CSR).

6. STUDY DESIGN

6.1. Study Description and Duration

This is an adaptive, phase 1/2/3, randomized, double-blinded, placebo-controlled master protocol to evaluate the efficacy, safety, and tolerability of REGN10933+REGN10987 combination therapy and REGN10989 monotherapy in outpatient (ie, ambulatory) adults with COVID-19.

To be eligible, adult patients must have laboratory-confirmed SARS-CoV-2 and COVID-19 symptoms but must not have been previously hospitalized or currently hospitalized (refer to Section 7.2 for study inclusion and exclusion criteria).

Phase 2 will initiate following IDMC clearance of a pooled phase 1 sentinel safety group across 2 studies (R10933-10987-COV-2066 and R10933-10987-COV-2067), and after initiation will enroll concurrently with phase 1. Once phase 2 is active, phase 1 will continue to enroll to completion, but phase 2 enrollment does not require the completion of phase 1 enrollment (for complete description and rationale for this process, refer to Section 3.2.1.1).

The schedule of events can be found in Table 1 (phase 1) and Table 2 (phase 2). See Figure 2 (phase 1) and Figure 3 (phase 2) for study flow diagrams. Additional information on study procedures can be found in Section 9.3.

Phase 1

On day 1, eligible patients in part A will be randomized to a single intravenous (IV) administration of REGN10933+REGN10987 (low dose), REGN10933+REGN1098 (high dose), REGN10989, or placebo. Patients will also have NP swab, nasal swab, and saliva samples taken and have blood drawn for safety, PK, ADA, and exploratory analyses.

In phase 1 part A, randomization will be limited to REGN10933+REGN10987 low dose, REGN10933+REGN10987 high dose, and placebo. In part B, randomization will be limited to REGN10989 and placebo (refer to Section 8.6 for more information on treatment arms and dosing). Part B will begin enrollment only after the FDA completes review of the IND application for REGN10989 and notifies the Sponsor that patients may be dosed with REGN10989 (eg, the Agency informs the Sponsor that it is safe to proceed).

Patients in phase 1 will be sequestered for the first 48 hours after dosing, during which time they will be closely monitored for SAEs and AESIs (Section 10). On day 3, patients can return home, if medically appropriate, after completing the day's assessments. Patients will have the option, if they choose, to remain sequestered until day 7. After completing assessments on day 7, all patients will be sent home, if medically appropriate.

Since patients will be sequestered and/or home quarantined for the duration of the study, assessments and sample collections may occur through a variety of methods. This may include (but is not limited to) visits at the study site or place of infusion, visits at the place of sequester, home-based visits (defined as visits by home health nurses, at mobile units, and/or testing centers), or by phone/telemedicine. Throughout the study, biological samples will be obtained by study personnel only at study locations where appropriate personal protective equipment (PPE) can be used.

Saliva and/or nasal samples will be collected every other day for the first 2 weeks and then approximately twice weekly thereafter. Nasopharyngeal swab samples will be collected on a similar, but less frequent, schedule. Patients will also have blood drawn during a subset of these visits.

Information regarding SAEs, AESIs, and medically-attended related due to COVID-19 will be recorded during weekly telemedicine and/or phone visits, and patients will be asked to notify study personnel as soon as possible about any medically-attended visits. Throughout the study, patients will also provide daily self-reported information about COVID-19 symptoms through an electronic survey.

The study will end on day 29, when patients will have final assessments conducted in person including NP swab, nasal swab, and saliva sample collections and blood draws for PK, ADA, and exploratory analyses.

Phase 2

On day 1, eligible patients will be randomized 1:1:1:1 to a single dose of REGN10933+REGN10987 (low dose), REGN10933+REGN10987 (high dose), REGN10989, or placebo. Patients will also have saliva and/or nasal samples taken, and have blood drawn for safety, PK, ADA, and exploratory analyses.

Patients will not be sequestered during phase 2. After infusion of study drug, patients will be observed for 2 hours and, if no SAEs or AESIs are observed, will be sent home.

Since patients will be quarantined at home, subsequent assessments and sample collections will potentially occur through a variety of in-person, home-based, and/or remote methods as described in phase 1.

Saliva and nasal samples will be collected every other day for the first 2 weeks and then approximately twice weekly thereafter. Information regarding SAEs, AESIs, and medically-attended visits related to COVID-19 will be recorded during weekly telemedicine and/or phone visits, and patients will be asked to notify study personnel as soon as possible about any medically-attended visits. Throughout the study, patients will also provide daily self-reported information about COVID-19 symptoms through an electronic survey.

On day 29, patients will have final assessments conducted in clinic, including saliva and nasal sample collection and blood draws for PK, ADA, and exploratory analysis.

Phase 3

The clinical efficacy endpoints, treatment arms, and final sample size for phase 3 are subject to change and will be informed by phase 2 data.

Prior to initiation of phase 3, enrollment may pause for IDMC review of phase 2.

Figure 2: Study Flow Diagram, Phase 1

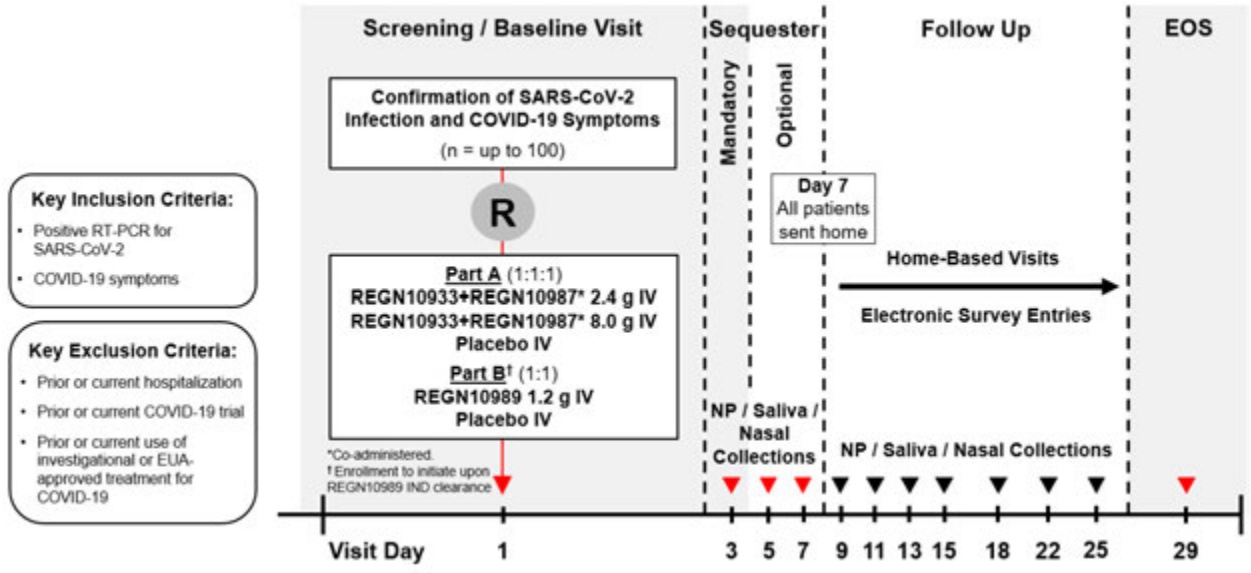
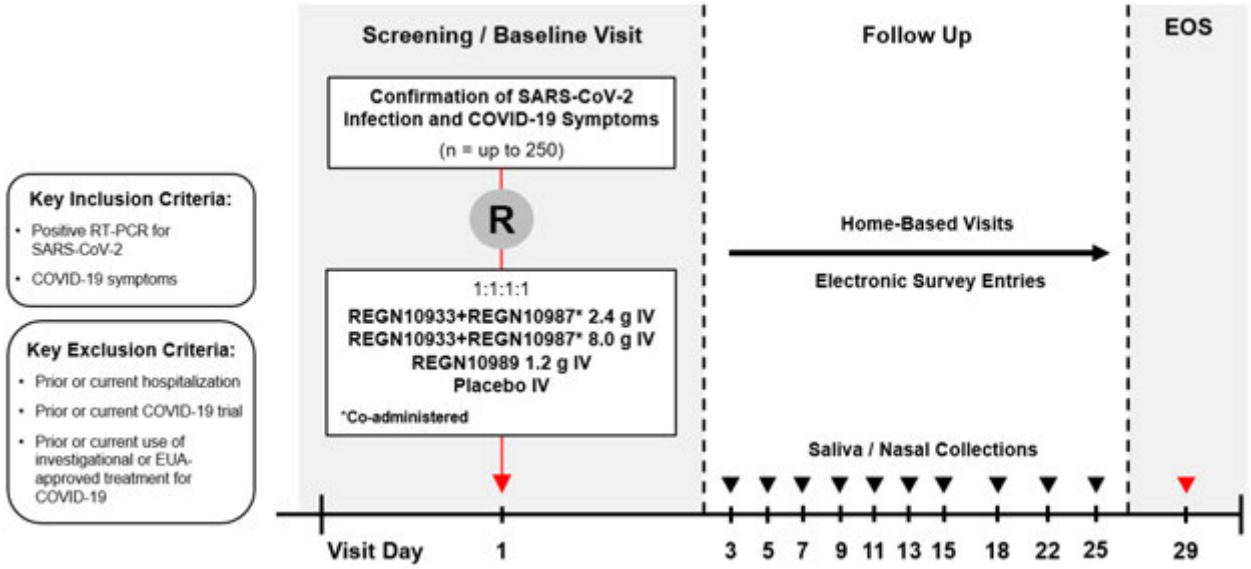


Figure 3: Study Flow Diagram, Phase 2



6.1.1. Study Stopping Rules

6.1.1.1. Individual Patient Stopping Rules

For an individual patient, the infusion rate can be slowed, interrupted, or stopped if there is a suspected drug-related event during the infusion suggestive of severe hypersensitivity or an infusion-related reaction, as per investigator discretion if it is deemed to be in the patient's best interest (see Section 8.5). As this is a single dose study, there are no other study drug discontinuation rules.

Patients stopping rules from the study include withdrawal of consent.

6.1.1.2. Study Stopping Criteria

The Sponsor may decide to stop or make adaptations to the study based upon the recommendations by an IDMC recommendations and review of the totality of evidence (see Section 6.2.1).

6.1.2. End of Study Definition

The end of study is defined as the date when the last living patient completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).

6.2. Study Committees

6.2.1. Independent Data Monitoring Committee

An IDMC will actively review data throughout the study to monitor safety of patients. The IDMC can make recommendations about early study closure or changes to the study conduct. Members of the IDMC will include 3 physicians with relevant medical specialty training and 1 statistician. The operation of the IDMC is governed by a charter describing further details, such as procedures (including but not limited to periodic safety monitoring) and requirements for reporting its observations to the Sponsor.

An IDMC will review pooled safety data through day 3 in the sentinel safety group as described in Section 3.2.1.1. In addition, the IDMC will conduct periodic data reviews, for instance, after all patients are enrolled into phase 1. Additional periodic reviews will be conducted during phase 2 and 3 of this study as detailed in the IDMC charter. These data reviews will include all available efficacy and safety data, including deaths, from all enrolled study participants up to the data cut point for the analysis. The IDMC will meet regularly throughout the course of the study to review safety data and make recommendations on study conduct.

6.2.2. Sponsor Review Committee

Periodic data reviews may be performed by selected unblinded senior Sponsor physicians and a statistician with no direct involvement in the study. Reviews will assess the totality of evidence and may be used to determine study adaptations (see Section 3.2.1.2).

6.3. Planned Interim Analysis

A description of the statistical methods to be employed is in Section 11.5, and blinding implications are discussed in Section 8.7.

Phase 1

An interim analysis is planned when all randomized patients in phase 1 have completed the day 7 visit. Safety and efficacy analysis for phase 1 will be performed when all randomized patients have completed the day 29 visit.

Virologic endpoints may be updated if there is extensive missing data on the chosen samples.

Phase 2

An interim analysis is planned when at least 50% of the randomized patients have completed the day 29 visit. The primary efficacy analysis for phase 2 will be performed when all randomized patients have completed the day 22 visit.

Phase 3

An interim analysis plan for phase 3 will be specified when adaptations for phase 3 are implemented in the study.

6.4. Periodic Data Reviews

Periodic reviews may be performed during phase 1 and phase 2 by selected unblinded senior Sponsor physicians and a statistician with no direct involvement in the study. Reviews will assess the totality of evidence and in phase 2 may be used to determine study adaptations (eg, whether to drop a dose arm).

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

Phase 1 will continue to enroll until up to 100 patients are randomized. Phase 2 will continue to enroll until up to 250 patients are randomized.

It is estimated that 704 patients (176 patients per arm) will be required for phase 3.

For information on the timing of enrollment, refer to Section 3.2.1.1. For treatment allocation and randomization, refer to Section 8.6.

7.2. Study Population

This study will enroll adult, non-hospitalized patients who have a positive RT-PCR test for SARS-CoV-2 and recent COVID-19 symptoms.

7.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Is male or female ≥18 years of age (or country's legal age of adulthood) at randomization
2. Has laboratory-confirmed SARS-CoV-2 infection (positive RT-PCR test) ≤72 hours of randomization
3. Is experiencing ≥1 of the following symptoms at randomization: fever, cough, shortness of breath
4. Has experienced COVID-19 symptoms for <7 days
5. Maintains O_2 saturation ≥93% on room air
6. Is willing and able to provide informed consent signed by study patient or legally acceptable representative
7. Is willing and able to comply with study procedures, including providing samples for viral shedding testing after discharge

7.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Has been admitted to a hospital prior to randomization, or is hospitalized (inpatient) at randomization, due to COVID-19
2. Has participated, or is participating, in a clinical research study evaluating COVID-19 convalescent plasma, monoclonal antibodies against SARS-CoV-2, or intravenous immunoglobulin (IVIG) within 3 months or less than 5 half-lives of the investigational product (whichever is longer) prior to the screening visit
3. Has a history of COVID-19 investigational or Emergency Use Authorization (EUA)-approved treatments in the past 30 days or less than 5 half-lives of the investigational

product (whichever is longer) prior to the screening visit. This includes, but is not limited to: remdesivir, hydroxychloroquine, tocilizumab, sarilumab, and other immunomodulatory agents

4. Current use of any COVID-19 investigational or EUA-approved treatment
5. Requires IVIG for medical condition other than COVID-19
6. Has known allergy or hypersensitivity to components of study drug
7. Has been discharged, or is planned to be discharged, to a quarantine center
8. Pregnant or breastfeeding women
9. Continued sexual activity in women of childbearing potential (WOCBP)* or sexually active men who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 6 months after the last dose.

   Highly effective contraceptive measures in women include:

   - Stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening,
   - Intrauterine device (IUD),
   - Intrauterine hormone-releasing system (IUS),
   - Bilateral tubal ligation,
   - Vasectomized partner,† and/or
   - Sexual abstinence.‡,§

   Male study participants with WOCBP partners are required to use condoms unless they are vasectomized† or practice sexual abstinence.‡,§

   * WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to Clinical Trial Facilitation Group (CTFG) guidance. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

   Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

   † Vasectomized partner or vasectomized study participant must have received medical assessment of the surgical success.

‡ Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

7.3. Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or Sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patient who are withdrawn prematurely from the study will be asked to complete an early termination visit and follow up contact, as described in Section 9.1.2.

7.4. Replacement of Patients

Patients prematurely discontinued from the study will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

Instructions on dose preparation are provided in the pharmacy manual. See Section 8.6 for the method of treatment allocation for each phase of the study.

- Co-administered REGN10933+REGN10987 combination therapy, 2.4 g (1.2 g each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 8.0 g (4.0 g each of REGN10933 and REGN10987) IV single dose
- REGN10989 monotherapy, 1.2 g IV single dose
- Placebo IV single dose

8.2. Background Treatment

No background treatment will be allowed. Patients may self-administer non-prescribed medications (eg, antipyretics).

8.3. Rescue Treatment(s)

Patients can receive rescue therapy for COVID-19 per local standard-of-care. Rescue treatment(s) will not be provided as part of the study.

8.4. Dose Modification and Study Treatment Discontinuation Rules

8.4.1. Dose Modification

This is a single dose study; dose modification is not allowed.

8.4.2. Study Drug Discontinuation

This is a single dose study; study drug discontinuation is not applicable.

8.5. Management of Acute Reactions

8.5.1. Acute Intravenous Infusion Reactions

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use if required for treatment. All grade ≥2 hypersensitivity reactions including infusion-related reactions (using the CTCAE severity scale specified in Section 10.2.4) must be reported as AESIs (see Section 10.2.2).

8.5.1.1. Interruption of the Intravenous Infusion

The infusion should be interrupted if any of the following adverse events are observed:

- Sustained/severe cough
- Rigors/chills

- Rash, pruritus (itching)
- Urticaria (hives, welts, wheals)
- Diaphoresis (sweating)
- Hypotension
- Dyspnea (shortness of breath)
- Vomiting
- Flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate.

If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

8.5.1.2. Termination of the Intravenous Infusion

The infusion should be terminated and **not** restarted if any of the following adverse events occur:

- Anaphylaxis*
- Laryngeal/pharyngeal edema
- Severe bronchospasm
- Chest pain
- Seizure
- Severe hypotension
- Other neurological symptoms (confusion, loss of consciousness, paresthesia, paralysis, etc)
- Any other symptom or sign that, in the opinion of the investigator, warrants termination of the IV infusion

*Consider anaphylaxis if the following is observed (Sampson, 2006): acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) **and at least one of the following:**

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

8.6. Method of Treatment Assignment

Patients will be randomized according to a central randomization scheme using an interactive web response system (IWRS).

Phase 1

In part A, 60 patients will be randomized in a 1:1:1 allocation ratio to one of the following:

- Co-administered REGN10933+REGN10987 combination therapy, 2.4 g (1.2 g each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 8.0 g (4.0 g each of REGN10933 and REGN10987) IV single dose
- Placebo IV single dose

In part B, 40 patients will be randomized in a 1:1 allocation ratio to one of the following:

- REGN10989 monotherapy, 1.2 g IV single dose
- Placebo IV single dose

In phase 1, randomization will not be stratified.

Phase 2

Patients will be randomized in a 1:1:1:1 allocation ratio to one of the treatments listed below, according to a central randomization scheme using an interactive web response system (IWRS).

- Co-administered REGN10933+REGN10987 combination therapy, 2.4 g (1.2 g each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 8.0 g (4.0 g each of REGN10933 and REGN10987) IV single dose
- REGN10989 monotherapy, 1.2 g IV single dose
- Placebo IV single dose

Randomization will be stratified by risk factors for hospitalization due to COVID-19:

- No risk factors for hospitalization due to COVID-19
- ≥1 risk factor for hospitalization due to COVID-19

The following are considered risk factors for the purposes of stratification (for rationale, refer to Section 3.2.1.4):

- Age >50 years
- Obesity, defined as BMI >30
- Cardiovascular disease, including hypertension
- Chronic lung disease, including asthma
- Chronic metabolic disease, including diabetes
- Chronic kidney disease, including those on dialysis
- Chronic liver disease

- Immunosuppressed, based on investigator's assessment (examples include: cancer treatment, bone marrow or organ transplantation, immune deficiencies, poorly-controlled HIV or AIDS, and prolonged use of corticosteroids or other immune-weakening medications)

Phase 3

The treatment arms, patient cohorts, sample size, and treatment allocation scheme for phase 3 will be finalized after review of phase 2 data.

8.7. Blinding

A pharmacist or qualified personnel at the site, not otherwise associated with the conduct of the study, will reconstitute the drug for IV administration. The drug infusion solution must be provided in identical form for active and placebo treatments, so that they remain indistinguishable to both study personnel and patients.

Study patients, the principal investigators, and study site personnel (with the exception of the unblinded pharmacist at each site) will remain blinded to all randomization assignments throughout the study. The Regeneron medical/study director, study monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all patient randomization assignments in phase 2 and phase 3.

Selected individuals from the Sponsor not involved in the conduct of the study may have access to unblinded phase 1 or phase 2 data as needed for safety review or other data review (see Section 6.2.2). The team performing the interim data reviews will be separate from the ongoing study team. No study personnel involved in the day-to-day conduct of the study will have access to any unblinded data before the database is locked for this study.

Anti-drug antibody, drug concentration, and biomarker results will not be communicated to the sites, and the Sponsor's blinded operational team will not have access to results associated with patient identification until after the database is locked.

8.8. Emergency Unblinding

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy) and when a treatment decision is contingent on knowing the patient's treatment assignment.

If unblinding is required:

- Only the investigator will make the decision to unblind the treatment assignment
- Only the affected patients will be unblinded
- The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind the patient. Unblinding is performed using the IVRS/IWRS which will notify Regeneron
- The investigator will notify Regeneron and/or designee as soon as possible after unblinding the patient

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency and when a treatment decision is contingent on knowing the patient's treatment assignment. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

8.9. Treatment Logistics and Accountability

8.9.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label unblinded investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

The unblinded pharmacist will prepare the unblinded investigational product and dispense it in a blinded manner to the blinded study staff for administration to the patient.

Study drug will be stored at the site at a temperature of 2ºC to 8ºC; Storage instructions will be provided in the pharmacy manual.

8.9.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed at the site with approval by the Sponsor or returned to the Sponsor or designee.

8.9.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication:

- Dispensed to each patient
- Returned from each patient (if applicable), and
- Disposed of at the site or returned to the Sponsor or designee.

All accountability records must be made available for inspection by the Sponsor and regulatory agency inspectors; photocopies must be provided to the Sponsor at the conclusion of the study.

8.9.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the Sponsor and regulatory agency inspectors.

8.10. Concomitant Medications

Any treatment administered from the first dose of study drug to the final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

For more information on recording of concomitant medications, refer to Section 9.3.4.3.

8.10.1. Prohibited and Permitted Medications

Patients are not permitted to receive any medication specified in the exclusion criteria for study enrollment (Section 7.2.2). Patients may otherwise continue their normal regimen of medications and procedures.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 1 (phase 1) and Table 2 (phase 2).

Table 1: Schedule of Events: Phase 1

Day	Screening/Baseline Visit[1]				Mandatory Sequester[2]		Optional Sequester[2]				Follow Up								EOS
	-1 to 1				2	3	4	5	6	7[2]	8	9	11	13	15	18	22	25	29
	Screen	Pre-Dose	Dose	Post-Dose															
Visit number	1				2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Visit Location: Place of Infusion (I), Place of Sequester (S), Home Based (H), Phone (P)[3]	*I*				*S*		*S or H*				*P*	*H*	*H*	*H*	*H, P*[4]	*H*	*H, P*[4]	*H*	*I*
Window (days)[5]												±1	±1	±1	±1	±1	±1	±1	±3
Screening/Baseline																			
Informed Consent	X																		
[redacted]	X																		
Inclusion/Exclusion	X																		
RT-PCR test for SARS-CoV-2[7]	X																		
Demographics	X																		
Medical History (incl. COVID-19 illness)	X																		
Weight and Height	X																		
Randomization		X																	
Treatment																			
Study Drug Administration			X																
Efficacy																			
Medically-Attended COVID-19 Visit Details										X					X		X		X
NP Swab for SARS-CoV-2 RT-qPCR		X				X		X		X		X		X			X		X
Saliva Sample for SARS-CoV-2 RT-qPCR		X				X		X		X		X	X	X	X	X	X	X	X
Nasal Swab for SARS-CoV-2 RT-qPCR		X				X		X		X		X	X	X	X	X	X	X	X
Safety																			
Vital Signs		X		X															
Treatment-emergent SAEs[8]			X	X	X	X	X	X	X	X	X				X		X		X
Grade ≥2 Hypersensitivity Reactions[8]			X	X	X	X	X	X	X	X	X				X		X		X
Grade ≥2 IRRs[8]			X	X	X	X	X												
Targeted Concomitant Medications[9]	X		X	X	X	X	X	X	X	X	X				X		X		X
Pregnancy Test (WOCBP)[10]	X																		X
Central Laboratory Testing																			
Hematology[11]	X[11]									X									X

Day	Screening/Baseline Visit[1]				Mandatory Sequester[2]		Optional Sequester[2]				Follow Up								EOS
	-1 to 1				2	3	4	5	6	7[2]	8	9	11	13	15	18	22	25	29
	Screen	Pre-Dose	Dose	Post-Dose															
Visit number	1				2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Visit Location: Place of Infusion (I), Place of Sequester (S), Home Based (H), Phone (P)[3]	*I*				*S*		*S or H*				*P*	*H*	*H*	*H*	*H, P*[4]	*H*	*H, P*[4]	*H*	*I*
Window (days)[5]												±1	±1	±1	±1	±1	±1	±1	±3
Blood Chemistry[11]	X[11]									X									X
Coagulation Tests[11]	X[11]									X									X
Central PK and Immunogenicity Testing																			
Serum for PK[12]		X[13]		X[13]		X		X		X					X				X
Serum for ADA[14]		X[14]																	X
Central Biomarker Testing																			
Serum for Serology		X				X				X									X
Serum for Cytokines		X				X				X									X
Serum for Research		X				X				X									X
Plasma for Complement		X				X				X									X
Plasma for Research		X				X				X									X
Exploratory Patient-reported Symptoms																			
SE-C19[15]		X		X	Daily														X
PGIS[15]		X		X	Daily														X
PGIC[15]																			X
[redacted]																			
[redacted]		[redacted]																	
[redacted]		[redacted]																	

ADA, anti-drug antibodies; EOS, end of study; IRR, infusion-related reaction; PGIC; Patient Global Impression of Change of symptoms associated with COVID-19; PGIS, Patient Global Impression of Severity of symptoms associated with COVID-19; NP, nasopharyngeal; [redacted] PK, pharmacokinetics; SAE, serious adverse event; RT-PCR, reverse transcription polymerase chain reaction; RT-qPCR, quantitative reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SE-C19, Symptom Evolution of COVID-19; WOCBP, women of childbearing potential.

Table 2: Schedule of Events: Phase 2

Day	Screening/Baseline Visit[1]				Follow Up													EOS
	-1 to 1				2	3	4	5	7	8	9	11	13	15	18	22	25	29
	Screen	Pre-Dose	Dose	Post-Dose														
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12	13	14	15
Visit Location: Place of Infusion (I), Home Based (H), Phone (P)[3]	*I*				*P*[4]	*H*	*H*	*H*	*H*	*P*[4]	*H*	*H*	*H*	*H, P*[4]	*H*	*H, P*[4]	*H*	*I*
Window (days)[5]	X									±1				±1		±1		±3
Screening/Baseline (in Person)																		
Informed Consent	X																	
[redacted]	X																	
Inclusion/Exclusion	X																	
RT-PCR test for SARS-CoV-2[7]	X																	
Demographics	X																	
Medical History (incl. COVID-19 illness)	X																	
Weight and Height	X																	
Randomization		X																
Treatment (in Person)																		
Study Drug Administration			X															
Efficacy (in Person or Telemedicine)																		
Medically-Attended COVID-19 Visit Details										X				X		X		X
Saliva Sample for SARS-CoV-2 RT-qPCR		X				X		X	X		X	X	X	X	X	X	X	X
Nasal Swab for SARS-CoV-2 RT-qPCR		X				X		X	X		X	X	X	X	X	X	X	X
Safety (in Person or Telemedicine)																		
Vital Signs		X		X														
Treatment-Emergent SAEs[8]			X	X	X	X	X			X				X		X		X
Grade ≥2 Hypersensitivity Reactions[8]			X	X	X	X	X			X				X		X		X
Grade ≥2 IRRs[8]			X	X	X	X	X											
Targeted Concomitant Medications[9]	X		X	X	X	X	X			X				X		X		X
Pregnancy Test (WOCBP)[10]	X																	X
Central Laboratory Testing (in Person)																		
Hematology[11]	X																	X
Blood Chemistry[11]	X																	X

Day	Screening/Baseline Visit[1]				Follow Up													EOS
	-1 to 1																	
	Screen	Pre-Dose	Dose	Post-Dose	2	3	4	5	7	8	9	11	13	15	18	22	25	29
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12	13	14	15
Visit Location: Place of Infusion (I), Home Based (H), Phone (P)[3]	*I*				*P*[4]	*H*	*H*	*H*	*H*	*P*[4]	*H*	*H*	*H*	*H, P*[4]	*H*	*H, P*[4]	*H*	*I*
Window (days)[5]	X									±1				±1		±1		±3
Coagulation tests[11]	X																	X
Central PK and Immunogenicity Testing (in Person)																		
Serum for PK[12]		X[13]		X[13]														X
Serum for ADA[14]		X[14]																X
Central Biomarker Testing (in Person)																		
Serum for Serology		X																X
Serum for Research		X																X
Plasma for Research		X																X
Exploratory Patient-reported Symptoms (Electronic)																		
SE-C19[15]		X		X	Daily													X
PGIS[15]		X		X	Daily													X
PGIC[15]																		X
[redacted]																		
[redacted]		[redacted]																
[redacted]		[redacted]																

ADA, anti-drug antibodies; ALT, alanine transaminase; AST, aspartate transaminase; CRP, c-reactive protein; CT, computed tomography EOI, end of infusion; EOS, end of study; IRR, infusion-related reaction; LDH, lactate dehydrogenase; NLR, neutrophil–lymphocyte ratio; PGIC; Patient Global Impression of Change of symptoms associated with COVID-19; PGIS, Patient Global Impression of Severity of symptoms associated with COVID-19; [redacted] PK, pharmacokinetics; SAE, serious adverse event; RT-qPCR, quantitative reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SE-C19, Symptom Evolution of COVID-19; WOCBP, women of childbearing potential.

9.1.1. Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2)

1. Screening visit may occur on the same day as, or the day prior to, the baseline visit.
2. **Phase 1 only:** Patients will be sequestered up to and including day 3. Patients have the option to leave sequester on day 4, or continue to remain sequestered until day 7. If medically appropriate, patients will be discharged on day 7 after indicated assessments have been completed. All samples and assessments indicated will be collected, regardless of location.
3. For a given day, the visit may occur at the place of infusion, place of sequester, as a home-based visit (defined as visits by home health nurses, at mobile units, and/or testing centers), or by phone/telemedicine as indicated.
4. **Phase 1:** On days 15, and 22 both home-based and phone visits will occur.

   Phase 2: On days 15 and 22, both home-based and phone visits will occur. Phone visit on day 8 is only required if patient returns home after mandatory sequester.
5. Visit windows are applicable only for visits in which samples are collected. Visits to collect information (eg, phone visits) will occur on the scheduled visit day.

[redacted]

7. Positive RT-PCR test will be obtained prior to randomization. Either rapid test (provided by Sponsor or locally) or prior documentation of positive test (≤72 hours) is acceptable. If prior test was conducted >72 hours from screening, RT-PCR must be repeated.
8. Only treatment-emergent SAEs and AESIs will be recorded in the eCRF.
9. Medications will be reviewed and recorded. Only the targeted medications listed in Section 9.3.4.3 will be recorded in the eCRF.
10. Pregnancy testing will be performed in women of childbearing potential (WOCBP) only. Negative pregnancy test must be confirmed prior to study drug administration. Serum or urine pregnancy test are both acceptable. Refer to Section 9.3.4.4 for more information on pregnancy testing and contraceptive measures.
11. Hematology, blood chemistry, and coagulation tests will be collected at the visits indicated and results will be entered in the eCRF. Hematology, blood chemistry, and coagulation tests must be collected prior to randomization. See Section 9.3.5 for details.
12. Actual dosing time and PK sample collection times will be recorded. Note that samples collected for PK can be analyzed, regardless of whether they are collected within the specified window.
13. At the screening/baseline visit, blood samples for PK assessment will be taken pre-dose and within 60 minutes after the end of infusion (EOI). The EOI sample should be collected from the arm contralateral to that used for IV infusion. If not medically feasible, the EOI sample can be drawn from the same arm, but not from the infusion catheter.

14. The window for predose ADA sample collection is as close to administration of study drug as is reasonable. Actual dosing times and ADA sample collection times will be recorded.
15. Patients will self-report symptoms using the SE-C19, PGIS, and PGIC electronic surveys. Order of completion will be as follows: SE-C19, PGIS, and PGIC (when applicable).

9.1.2. Early Termination: Early Termination Visit and Follow-up Contact

Patients who are withdrawn from the study will be asked to provide a final blood draw sample for PK analysis and to have a follow-up contact by phone at the end of study.

9.2. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of treatment-emergent SAEs or AESIs, or for any other reason, as warranted.

9.3. Study Procedures

This section describes the procedures and collections that will be performed in this study. Procedures and collections will occur according to the schedule of events (Table 1 and Table 2).

9.3.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population.

9.3.1.1. Informed Consent

Informed consent must be obtained according to the requirements described in Section 13.2. [redacted]

9.3.1.2. RT-PCR Test for SARS-CoV-2

The investigator or sub-investigator will verify that the patient has tested positive for SARS-CoV-2 by RT-PCR and record the local testing result, specimen type, assay type, and date of the test in the eCRF. If local RT-PCR testing was performed >72 hours prior to screening, a new test is required for study inclusion

9.3.1.3. Demographics

Refer to Section 5.1.

9.3.1.4. Medical History

Medical history will include the following:

- Prior and current symptoms related to COVID-19
- Risk factors for hospitalization due to COVID-19, as defined in Section 8.6
- Whether the patient will be receiving oxygen at home by nasal cannula
- Menopausal history

9.3.1.5. Weight and Height

Weight and height will be recorded at the screening/baseline visit.

9.3.2. Treatment

See Section 8.1.

9.3.3. Efficacy Procedures

9.3.3.1. Nasopharyngeal, Nasal Swab, and Saliva Sample Collection

Nasal swab, saliva samples, and will be used to collect secretions from patients to determine presence or absence of SARS-CoV-2 virus and to measure viral shedding. In phase 1, NP samples will also be collected.

Samples will be used for RT-qPCR analysis. Samples may additionally be used for exploratory viral RNA sequencing (NP, nasal swab, saliva) and/or viral culture (NP, nasal swab).

Additional details regarding sample collection and analysis can be found in the laboratory manual.

9.3.3.2. Medically-Attended COVID-19 Visit Details

Details associated with any medically-attended visit will be recorded in the eCRF. This will include at minimum:

- Nature of the visit (telemedicine, urgent care, other outpatient, hospital, EC, ICU)
- Date and length of visit
- If hospitalized, whether the primary reason for hospitalization is related to COVID-19
- If outpatient medically-attended visit, whether the primary reason for the visit is related to COVID-19

COVID-19 related medically-attended visit will be defined as: hospitalization with the primary reason for hospitalization being COVID-19, or an outpatient visit (including a visit to the ER, UCC, doctor's office, or telemedicine visit) with the primary reason for the visit being COVID-19.

During the 48-hour sequestration period (phase 1 only), medically-attended visits will include any transfer of a patient from the phase 1 clinic/research unit/quarantine site to a setting indicative of worsening COVID-19 (eg, admission to an ER or hospital).

9.3.4. Safety Procedures

9.3.4.1. Vital Signs

Vital signs will include blood pressure, heart rate, respiration rate, and temperature.

Blood pressure should be measured after the patient has been resting quietly for at least 5 minutes and may be obtained from a seated or supine position.

9.3.4.2. Serious Adverse Events and Adverse Events of Special Interest

Serious adverse events (as defined in Section 10.2.1) and AESIs (as defined in Section 10.2.2) will be recorded.

Note that any symptoms collected by SE-C19, PGIC, or PGIS (Section 9.3.9) will not be considered adverse events.

9.3.4.3. Record Targeted Concomitant Medications

A targeted list of the following concomitant medications will be recorded:

- Putative COVID-19 treatment
- Antipyretics, such as aspirin, acetaminophen, ibuprofen, and other non-steroidal anti-inflammatory drugs (NSAIDs)
- Warfarin or other anti-thrombotic drugs
- Cyclosporine A
- Theophylline
- Digoxin
- Antiepileptics, such as carbamazepine (Carbatrol®, Tegretol®), divalproex (Depakote®), phenytoin (Dilantin®), valproic acid (Depakene®);
- Antiarrhythmics, such as disopyramide (Norpace®), procainamide (Procan®, Pronestyl®), quinidine (Quinidex®, Quin Release Quin-G®)
- Antivirals, antibacterial, and antifungals
- Anti-parasitics
- Interferon beta
- Corticosteroids
- Angiotensin receptor blockers, such as Azilsartan (Edarbi®), Candesartan (Atacand®), Eprosartan (Teveten®), Irbesartan (Avapro®), Losartan (Cozaar®), Olmesartan (Benicar®), Telmisartan (Micardis®), Valsartan (Diovan®)
- Angiotensin converting enzyme inhibitors: benazepril (Lotensin®), captopril (Capoten®), enalapril (Vasotec®), fosinopril (Monopril®), lisinopril (Prinivil®, Zestril®), moexipril (Univasc®), perindopril (Aceon®), quinapril (Accupril®)

For more information on concomitant medications, refer to Section 8.10.

9.3.4.4. Pregnancy Test for Women of Childbearing Potential

Pregnancy testing may be satisfied by either serum pregnancy test or by urine β-HCG. Pregnancy tests are a requirement for WOCBP only. Pregnancy test will be performed at the local laboratory.

WOCBP and female partners of male patients will be advised to use highly-effective contraception for 6 months after the receiving study drug (see Section 7.2.2).

9.3.5. Laboratory Testing

Hematology and blood chemistry will be analyzed by a central laboratory. Detailed instructions are provided in the laboratory manual.

Blood Chemistry

Tests will include:

Sodium	Blood urea nitrogen (BUN)	Alkaline phosphatase
Potassium	Aspartate aminotransferase (AST)	Creatinine
Chloride	Alanine aminotransferase (ALT)	Creatine phosphokinase (CPK)
Carbon dioxide	Total bilirubin	Lactate dehydrogenase (LDH)
Glucose	Albumin	C-reactive protein
D-dimer	Ferritin	

Hematology

Tests will include:

Hemoglobin	Differential:	Neutrophils
Hematocrit		Lymphocytes
Red blood cells (RBCs)		Monocytes
White blood cells (WBCs)		Basophils
Platelet count		Eosinophils

Other Laboratory Tests

Coagulation tests: Prothrombin time (PT/INR), partial thromboplastin time (PTT)

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the Medical/Study Director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as treatment-emergent SAEs are provided in Section 10.1.1.

9.3.6. Drug Concentration and Measurements

Samples for PK assessment will be collected at the timepoints indicated in the schedule of events.

Any unused samples may be kept for up 15 years after study completion for use in exploratory research.

9.3.7. Immunogenicity Measurements and Samples

Samples for ADA assessment will be collected at the timepoints listed in the schedule of events.

Any unused samples may be kept for up 15 years after study completion for use in exploratory research.

9.3.8. Exploratory Pharmacodynamic/Biomarker Analyses

9.3.8.1. Hematology for Complete Blood Count and Differential

Exploratory biomarkers including the neutrophil-lymphocyte ratio (NLR) will be assessed. Neutrophil-lymphocyte ratio is as an inflammatory biomarker and is suggested to be an independent risk factor of the in-hospital mortality for COVID-19 patients. Assessment of NLR trends may help identify individuals with COVID-19 at higher risk of complications (Liu, 2020) (Qin, 2020). We will measure NLR as an exploratory endpoint and, as compared to placebo, and association with clinical endpoints will be evaluated.

9.3.8.2. Serum and Plasma Biomarkers

Changes in circulating concentrations of serum/plasma biomarkers associated with inflammation and disease progression will be assessed in REGN10933+REGN10987 and/or REGN10989 groups as compared to the placebo group in phase 1 and phase 2. The association between changes in disease related biomarkers with clinical endpoints will be evaluated.

Biomarkers to be assessed may include, but not be limited to, the following:

C-reactive protein (CRP), lactate dehydrogenase (LDH), D-Dimer, and ferritin will be assessed as exploratory endpoints. CRP is a general inflammation marker that is increased and tracks with severity of COVID-19 and lung lesions. CRP is associated with adverse outcomes including supplemental O_2 requirement and death (Luo, 2020) (Qin, 2020) (Ruan, 2020) (Wang, 2020b) (Young, 2020). LDH was identified as a predictive factor for early recognition of lung injury and advanced COVID-19 cases (Han, 2020) and will be assessed as part of the clinical chemistry panel. Ferritin is a general inflammation marker that is associated with severity of COVID-19 (Qin, 2020). D-dimer levels greater than 1 µg/mL have been reported to identify patients with poor prognosis at an early stage (Zhou, 2020).

9.3.8.3. Virology

Viral Sequencing

In support of public health initiatives to track SARS-CoV-2 genetic variants, as well as to monitor for possible viral resistance, viral genome sequencing will be performed on viral nucleic acid isolated from nasopharyngeal, nasal swab, and/or saliva samples.

Viral Resistance

Patients will be assessed for virologic resistance, defined as a positive RT-qPCR test at the EOS visit, an inability to reach 2 consecutive negative RT-qPCR assessments by day 29, or 2 consecutive negative RT-qPCR tests with subsequent viral load at detectable limits with positive RT-qPCR at the EOS visit. For patients who exhibit viral resistance, viral sequencing will be assessed to understand the potential relationship between genetic mutations and mAb functional activity.

Viral Infectivity

In vitro SARS-CoV-2 infectivity of cultured cells will be explored using NP and/or nasal swab samples. Infectivity of cells grown in culture will be assessed by plaque forming unit (PFU) assays and/or immunofluorescence assays. We may also use sub-genomic viral RNA transcript assays or

other measures of in vivo infectivity. Viral sub genomic mRNA is transcribed only in infected cells and is not packaged into virions, and is therefore an indicator of actively-infected cells. These various infectivity data may be associated with RT-qPCR data.

9.3.8.4. Serological Immunoassays for Anti-SARS-CoV2 Antibodies

In order to explore the impact of a baseline humoral activity SARS-CoV2 on the response to REGN10933+REGN10987, and/or REGN10989, anti-SARS-CoV2 antibodies in serum will be assayed in serological immunoassays detecting antibodies against the S protein and/or the N protein will be measured. Association of baseline serology results with clinical endpoints will be evaluated. To evaluate the effects of REGN10933+REGN10987, and/or REGN10989, on generation of a humoral immune response to SARS-CoV2, anti-SARS-CoV2 N antibodies in serum will be measured.

9.3.8.5. Serum and Plasma for Research

COVID-19, SARS-CoV-2, REGN10933+REGN10987, REGN10989, host and viral biological pathways and mechanisms related disease activity and clinical outcomes. Analyses on serum and plasma for research may include but are not limited to the following analyses.

Complement

As complement activation has been hypothesized to contribute to the maladaptive inflammatory response seen in some patients with advanced COVID-19, circulating complement biomarker concentrations may be assessed in order to understand the involvement of the classical and lectin and/or alternative complement pathways in the pathogenesis of COVID-19 and clinical outcomes.

Cytokines

The initial inflammatory responses to an infection are rapid and non-specific, regulated by proinflammatory cytokines such as interleukin-6 (IL-6). As IL-6 has been implicated in the severity of COVID-19, IL-6 and other cytokines including, but not limited to, IL-8, IL-1β and IFNγ may be measured in phase 2. Additional cytokines may be interrogated by use of cytokine panels.

The data from these exploratory analyses of complement and cytokines may not be included in the CSR.

9.3.9. Exploratory Patient-Reported Symptoms

Patients will provide self-reported symptoms using the Symptom Evolution of COVID-19 (SE-C19) instrument. This electronic survey was developed de novo by Regeneron as a means to better understand the symptomatic course of COVID-19 infection over time and is based on the current available evidence on symptoms of COVID-19 (CEBM) (Arentz, 2020) (Chen, 2020a) (Chen, 2020b) (Huang, 2020) (Song, 2020) (Wang, 2020a). Patients will self-report symptoms using a compatible electronic device (eg, smartphone, tablet, laptop or personal computer). For each symptom, patients will be asked to rate their experience as mild, moderate, or severe at the worst moment within the last 24 hours.

To aid interpretation, the SE-C19 will be supplemented by 2 brief scales, the Patient Global Impression of Change (PGIC) and the Patient Global Impression of Severity (PGIS) scales, which assess the overall subjective experience of symptom severity and change in symptoms over time.

As a representation of the current available evidence of COVID-19 symptoms, the SE-C19 appears to have face validity for tracking symptom onset, severity, and recovery, content validity will be confirmed by an interview-based study of patients and clinicians.

Note that any symptoms collected by SE-C19, PGIS, or PGIC will not be considered adverse events and will not be reconciled with any adverse events.

[redacted]

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record treatment-emergent SAEs and AESIs (as defined in Section 10.1.3) occurring during the study data collection, beginning from the pretreatment period until the end of the observation period (see Section 11.4.5.1). Medical conditions that existed or were diagnosed prior to the signing of the informed consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of informed consent should also be recorded as medical history. Throughout the study, the investigator will determine whether any treatment-emergent SAEs and AESIs have occurred by evaluating the patient. These events may be directly observed, reported spontaneously by the patient, or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all serious TEAEs and AESIs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The investigator's assessment must be clearly documented in the site's source documentation with the investigator's signature. The investigator should follow up on treatment-emergent SAEs and AESIs until they have resolved or are considered clinically stable.

Always report the diagnosis as the SAE or AESI term. When a diagnosis is unavailable, report the primary sign or symptom as the SAE or AESI term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of SAE or AESI.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the investigator to determine their clinical significance and whether they fulfil the criteria of SAEs and AESIs and will need to be reported.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an SAE, but the reason for the procedure may be an SAE. Pre-planned (prior to signing the informed consent form [ICF]) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur subsequent to the reporting period (end of study) that the investigator assesses as related to study drug should also be reported.

All treatment-emergent SAEs, AESIs, and pregnancy reports are to be reported according to the procedures in Section 10.1.3.

10.1.2. Reporting Procedure

All treatment-emergent SAEs and AESIs must be reported with investigator's assessment of the event's seriousness, severity, and causality to the blinded study drug. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the SAE/AESI eCRF. Specific or estimated dates of event onset, treatment, and

resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc) will be summarized in the narrative on the SAE/AESI eCRF and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.1.3. Events that Require Expedited Reporting to Sponsor

The following events also require reporting to the Sponsor (or designee) within 24 hours of learning of the event:

- **Treatment-emergent SAEs**.
- **AESI** (serious and nonserious)**:** AESI for this study are:
  - Grade ≥2 infusion-related reactions
  - Grade ≥2 hypersensitivity reactions
- **Pregnancy:** Although pregnancy is not considered an adverse event, it is the responsibility of the investigator to report to the Sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female study patient or female partner of a male study patient for up to 6 months after the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the Sponsor.

10.2. Definitions

10.2.1. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an adverse event that had occurred in a more severe form, might have caused death.
- Requires in-patient **re-hospitalization** (readmission after discharge) or **prolongation of existing hospitalization**. In-patient hospitalization is defined as a hospital admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event or is prolonged due to the development of a new adverse event as determined by the investigator or treating physician.

- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** – Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events.

10.2.2. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical interest specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

Adverse events of special interest for this study are defined in Section 10.1.3.

10.2.3. Infusion Reactions

Infusion-related reactions are defined as any relevant adverse events that occurs during the infusion or up to day 4.

Hypersensitivity reactions are defined as any relevant adverse event that occurs during the infusion or up to study day 29.

10.2.4. Severity

The severity of adverse events (including test findings classified as adverse events) will be graded using the current version of the NCI-CTCAE v5.0 (Division of Cancer Treatment and Diagnosis [DCTD], 2020).

Treatment-emergent SAEs or AESIs not listed in the NCI-CTCAE will be graded according to the scale in Table 3.

Table 3: NCI-CTCAE General Grading System (v5.0)

not bedridden.

Grade	Severity	Description
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate	Minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)*
3	Severe	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[†]

Grade	Severity	Description
4	Life-threatening	Life threatening consequences; urgent intervention indicated
5	Death	Death related to adverse events

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
† Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

10.2.5. Causality

The investigator must provide causality assessment as whether or not there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset versus time drug was administered
- Nature of the reactions: immediate versus long term
- Clinical and pathological features of the events
- Existing information about the drug & same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Patient's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The adverse event follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The adverse event follows a reasonable temporal sequence from study drug administration and is a known reaction to the drug under study or its class of drugs or is predicted by known pharmacology.
- Not Related:
  - The adverse event does not follow a reasonable sequence from study drug administration or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol specified procedure):

- Related:
  - The adverse event follows a reasonable temporal sequence from a protocol specified procedure and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The adverse event does not follow a reasonable sequence from a protocol specified procedure or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

10.3. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the Sponsor in a timely fashion. The Sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Global Patient Safety; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

10.4. Notifying Health Authorities, Institutional Review Board, Ethics Committee, and Investigators

During the study, the Sponsor and/or the CRO will inform health authorities, ECs/Institutional Review Board (IRBs), and the participating investigators of any SUSARs (Suspected Unexpected Serious Adverse Reactions) occurring in other study centers or other studies of the active study drug, as appropriate per local reporting requirements. In addition, the Sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

Upon receipt of the Sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the IRB/EC unless delegated to the Sponsor.

Event expectedness for study drug is assessed against the Reference Safety Information section of the Investigator's Brochure that is effective for expedited safety reporting.

At the completion of the study, the Sponsor will report all safety observations made during the conduct of the trial in the Clinical Study Report to health authorities and ECs/IRB as appropriate.

11. STATISTICAL PLAN

This section provides the basis for the statistical analysis plans (SAP) for the study. The SAPs may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAPs will be issued before the first database lock in each portion of the study.

This master protocol is intended to allow for adaptations, including: dropping of a treatment group; addition of new treatment arms with other anti-SARS-CoV-2S protein mAbs as they become available for clinical testing; determination of the primary endpoints for phase 3; and sample size re-estimation for phase 2 and 3. Therefore, treatment groups in phase 3 and analyses for the phase 3 portion will depend on the final endpoints and treatment groups selected based on phase 2 results.

The phase 3 portion will be powered and analyzed independently of the phase 2 portion, in order to ensure that the phase 3 portion is confirmatory and to avoid inflating type I error rate in the phase 3 portion of the study.

Endpoints are listed in Section 3.2.2. Analysis variables are listed in Section 5.

11.1. Statistical Hypothesis

The statistical hypotheses for the primary efficacy endpoints for the phase 1 and phase 2 portion of the study are as follows:

- There is no treatment difference between REGN10933+REGN10987 2.4 g IV and placebo in terms of time weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22 versus there is a treatment difference
- There is no treatment difference between REGN10933+REGN10987 8.0 g IV and placebo in terms of time weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22 versus there is a treatment difference
- There is no treatment difference between REGN10989 1.2 g IV and placebo in terms of time weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22 versus there is a treatment difference.

The safety and tolerability objectives of phase 1 will be evaluated by estimating the proportion of patients with treatment-emergent SAEs through day 29 and hypersensitivity reactions (grade ≥2) including infusion-related reactions through day 29.

11.2. Justification of Sample Size

The sample size is based on the primary virologic endpoint of time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, using a two-sample t-test at a two-sided significance of α=0.05.

Due to lack of published data on the variation of time-weighted average change from baseline in viral shedding in COVID-19, the standard deviation of actual viral shedding values at a timepoint from the literature was used for sample size calculation. Blinded sample size re-estimation will be performed to assess the assumed standard deviation of primary virologic endpoint.

Assuming standard deviation of 2.1 log_{10} copies/mL (Cao, 2020), a sample size of 20 patients per arm in phase 1 will have at least 80% power to detect a difference of 1.91 log_{10} copies/mL. The smallest treatment difference that will result in $p<0.05$ is approximately 1.34 log_{10} copies/mL. A total sample size of 100 patients is planned for phase 1 including 60 patients randomized to placebo and the 2 REGN10933+REGN10987 combination therapies and 40 patients randomized concurrently to placebo and REGN10989 monotherapy when it is available.

Assuming a 10% dropout rate and standard deviation of 2.1 $\log_{10}$ copies/mL (Cao, 2020), a sample size of 50 patients per arm in phase 2 will have at least 80% power to detect a difference of 1.25 $\log_{10}$ copies/mL. If a standard deviation of 3.8 $\log_{10}$ copies/mL is assumed (Wang, 2020c), the detectable difference would be 2.27 $\log_{10}$ copies/mL. A total sample size of up to 250 patients are needed including 150 patients randomized to placebo and the 2 REGN10933+REGN10987 combination therapies when phase 2 starts, and up to 100 patients randomized concurrently to placebo and REGN10989 monotherapy when it is available. For the clinical endpoint of proportion of patients with ≥1 COVID-19 related medically-attended visit, assuming a 30% rate in the control arm, the smallest treatment difference that will result in $p<0.05$ is approximately 17%.

The initial estimate of the sample size for phase 3 is based on the phase 3 primary endpoint of proportion of patients with ≥1 COVID-19 related medically-attended visit. Assuming a 10% dropout rate and 30% rate of patients with ≥1 COVID-19 related medically-attended visit in the control arm, a sample size of 704 patients (176 patients per arm) will have at least 90% power to detect a 50% reduction of the control rate (to 15%) in the treatment arm.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

The full analysis set (FAS) includes all randomized patients and is based on the treatment allocated (as randomized). Efficacy endpoints will be analyzed using the FAS.

11.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any study drug; it is based on the treatment received (as treated). Determination of "as treated" will be based on the actual study drug received on day 1. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

11.3.3. Pharmacokinetic Analysis Sets

The PK analysis population includes all patients who received any study drug and who had a at least 1 non-missing result following the first dose of study drug. Patients will be analyzed based on actual treatment received.

11.3.4. Immunogenicity Analysis Sets

The ADA analysis set includes all patients who received study drug and had at least 1 non-missing ADA result from the ADA assay after first dose of the study drug. Patients will be analyzed according to the treatment actually received.

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

Statistical analyses will be performed using Statistical Analysis Software (SAS) Version 9.4 or higher.

11.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the ICF
- The total number of randomized patients: received a randomization number
- The total number of patients who discontinued the study, and the reasons for discontinuation
- The total number of patients who discontinued from study treatment, and the reasons for discontinuation
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics including medical history will be summarized descriptively for each phase by treatment group, and by all patients combined.

11.4.3. Efficacy Analyses

11.4.3.1. Primary Efficacy Analysis

The primary efficacy variable for phase 1 and phase 2 is time-weighted average change from baseline in viral shedding from day 1 to day 22. The estimand for the primary hypothesis is the difference in means between each of the anti-spike SARS-CoV-2 mAb treatments and placebo in the primary efficacy variable in the FAS. Data collected after use of convalescent serum therapy will be excluded from efficacy analysis. All other available data will be used in the analysis regardless of intercurrent events such as rescue medication or discontinuation, ie, treatment policy approach.

Before calculating the primary efficacy variable, missing viral shedding values with less than the lower limit of quantification of the PCR assay but with positive qualitative results are imputed with half of lower limit of quantification of the PCR assay; missing values with negative RNA are imputed with 0 $\log_{10}$ copies/mL. The primary efficacy variable will be calculated using trapezoidal rule, ie, area under the curve for change from baseline at each time point from day 1 to last observation divided by the number of days from day 1 to day of last observation. The primary efficacy variable is analyzed using an Analysis of Covariance (ANCOVA) model with treatment group and randomization strata as fixed effects and baseline viral shedding as covariate.

The least squares means estimates for the time-weighted average mean change from baseline in viral shedding for each treatment group, as well as the difference between each anti-spike mAb

treatment arm and placebo, will be presented along with the corresponding p-value, standard error, and associated 95% confidence interval.

Sensitivity analysis may be performed to include all available data including data collected after use of convalescent serum therapy. Other sensitivity analyses may be conducted and will be specified in the SAP.

The phase 3 primary efficacy variable is the proportion of patients with medically attended visits due to worsening COVID-19 symptoms and signs and will be compared between groups using stratified Cochran-Mantel-Haenszel test at two-sided 0.05 level. P-values and 95% confidence intervals for the treatment difference will be presented.

11.4.3.2. Secondary Efficacy Analysis

For phase 1 and phase 2, time-weighted average change from baseline in viral shedding (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in other type of samples such as nasal samples, will be analyzed using the same method as the primary efficacy endpoint.

Time to event endpoints including time to negative PCR results will be analyzed using the stratified log-rank test with randomization strata as a stratification factor. Estimates of difference in median times and associated 95% confidence intervals using Kaplan-Meier method will be reported. The hazard ratio and its 95% CI will be estimated by Cox regression model with terms for treatment group and randomization strata. P-value from the stratified log-rank test will be reported.

All proportion endpoints including the proportion of patients with medically attended visits due to worsening COVID-19 for phase 1 will be summarized descriptively. Difference in proportions between each anti-spike mAb treatment arm and placebo will be presented descriptively along with 95% confidence interval.

All proportion endpoints including the proportion of patients with medically attended visits due to worsening COVID-19 for phase 2 will be compared between groups using stratified Cochran-Mantel-Haenszel (CMH) test at two-sided 0.05 level. P-values and 95% stratified Newcombe confidence intervals with CMH weights for the treatment difference will be presented.

The total number of COVID-19 related medically-attended visits and days of hospitalization due to COVID-19 will be summarized descriptively. To assess the time course of treatment effect in viral shedding, the change from baseline in viral shedding at each visit will be analyzed using a mixed-effect model for repeated measures (MMRM) with terms for baseline, randomization strata, treatment, visit, and treatment-by-visit interaction. Within-patient errors will be modeled with an unstructured, heterogeneous autoregressive (1), or compound symmetry covariance matrix in that order if a model does not converge. The least squares means estimates for the mean at each visit and mean change from baseline to each visit as well as the difference of these estimates between each anti-S mAb treatment arm and placebo will be provided along with the corresponding standard error, p-value, and associated 95% confidence interval.

Other continuous variables including change from baseline in SE-C19 score will be analyzed using the similar MMRM method.

Subgroup analysis for the primary efficacy endpoint and selected secondary endpoints for phase 2 may be performed by randomization strata and other factors if deemed appropriate.

11.4.4. Control of Multiplicity

There will be no control for multiplicity for phase 1 data analyses. Appropriate multiplicity adjustment will be applied to control for multiple comparisons and maintain study-wise Type I error rate at a two-sided 0.05 level for the phase 2 and phase 3 portions of the study and detailed in the SAP.

11.4.5. Safety Analysis

11.4.5.1. Adverse Events

Definitions

For safety variables, 2 periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before study drug administration
- The observation period is defined as the time of study drug administration to the last study visit

Treatment-emergent SAEs and AESIs are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the observation period.

Analysis

All SAEs and AESIs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The preferred term (PT), and the primary system organ class (SOC) will be listed.

Phase 1 primary safety analysis

Summaries by treatment group will include the following:

- The number (n) and percentage (%) of patients with at least 1 treatment-emergent serious adverse events (SAEs) through day 29 by system organ class and PT
- The number (n) and percentage (%) of patients with at least 1 infusion-related reactions (grade ≥2), through day 4 by PT
- The number (n) and percentage (%) of patients with at least 1 hypersensitivity reactions (grade ≥2), through day 29 by PT

For each phase, summaries of SAEs and AESIs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 event by SOC and PT
- SAEs and AESIs by severity (according to the grading scale outlined in Section 10.2.4), presented by SOC and PT
- SAEs and AESIs by relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent SAEs and AESIs

Deaths, SAEs and AESIs will also be listed.

11.4.5.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of patients with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized for each clinical laboratory test for all patients and separately for patients in whom the PCSV criterion was normal or missing at baseline.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out of laboratory range values.

11.4.5.3. Treatment Exposure

The number and percentage of patients randomized and exposed to double-blind study drug, and duration of exposure to treatment during the study will be presented by treatment group.

11.4.5.4. Treatment Compliance

Treatment compliance in terms of total dose and infusion interruption will be summarized. The analysis methods will be detailed in the SAP.

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

Phase 1 (Dense Sampling)

The PK parameters may include, but are not limited to C_{max}, C_{max}/dose, t_{max}, and AUC_{last}.

The concentrations of REGN10933, REGN10987, and REGN10989 in serum over time and selected pharmacokinetic parameters will be summarized descriptively for each of the treatment groups.

Phase 2 (Sparse Sampling)

The concentrations of REGN10933, REGN10987, and REGN10989 in serum over time will be summarized descriptively for each of the treatment groups

11.4.7. Pharmacokinetics and Pharmacokinetics/Pharmacodynamics Analyses

Exposure-response analyses for select efficacy and safety endpoints and/or biomarkers may be performed, as appropriate.

11.4.8. Analysis of Immunogenicity Data

Immunogenicity will be characterized by the ADA responses and titers observed in subjects in the ADA analysis set. ADA response categories and titer categories are defined as follows:

ADA Response Categories:

- ADA Negative, defined as ADA negative response in the ADA assays for all time points regardless of any missing samples
- Pre-existing immunoreactivity, defined as either an ADA positive response in the ADA assay response at baseline with all post first dose ADA results negative, or a positive assay response at baseline with all post first dose ADA assay responses less than 9-fold over baseline titer levels.
- Treatment-emergent response, defined as an ADA positive response in the ADA assay post first dose when baseline results are negative or missing.
- Treatment boosted ADA response, defined as a positive response in the ADA assay post first dose that is greater than or equal to 9-fold over baseline titer levels when baseline results are positive

Titer categories (Maximum titer values):

- Low (titer <1,000)
- Moderate (1,000 ≤ titer ≤10,000)
- High (titer >10,000)

The following analysis will be provided:

- Number (n) and percent (%) of ADA-negative subjects (pre-existing immunoreactivity or negative in the ADA assay at all time points) by treatment groups
- Number (n) and percent (%) of treatment-emergent ADA positive subjects by treatment groups and ADA titer categories and at the
- Number (n) and percent (%) of treatment-boosted ADA positive subjects/patients by treatment groups and ADA titer categories

Listing of all ADA titer levels will be provided for subjects/patients with pre-existing, treatment-emergent and treatment-boosted ADA response.

11.5. Interim Analysis

An interim analysis is planned when all randomized patients in phase 1 have completed the day 7 in-clinic visit. Safety and efficacy analyses for phase 1 will be performed when all randomized patients have completed the day 29 visit.

For phase 2, an interim analysis is planned when at least 50% of the randomized patients have completed the day 29 visit. Non-binding O'Brien-Fleming boundaries for efficacy and futility will be used as a guide to monitor the primary efficacy endpoint at an overall two-sided type-I error rate of 0.05. Bayesian predictive probability based on non-informative prior will be provided as

an additional guide for futility monitoring. Bayesian predictive probability allows computation of the probability of obtaining a positive result by the end of the trial given observed data. If the predictive probability is less than 10%, it suggests a low probability of having a positive result for the dose arm at the end of the study. The primary efficacy analysis for phase 2 will be performed when all randomized patients have completed the day 22 visit. Based on the interim and phase 2 analyses, 1 or 2 dose arms may be dropped. The interim analysis will be detailed in the SAP.

Timing and details of interim analysis for phase 3 will be provided and appropriate Type I error control will be applied once phase 3 study design is determined based on review of phase 2 data. Virologic endpoints may be updated if there is extensive missing data on the chosen samples.

11.6. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and Sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the Sponsor is responsible for quality assurance to ensure that the study is conducted, and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing) will be maintained and stored at Regeneron (Sponsor).

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, SAEs, baseline findings, medication, medical history) will be done using internationally recognized and accepted dictionaries.

The eCRF data for this study will be collected with an electronic data capture (EDC) Medidata Rave.

12.1.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IWRS system – randomization, study drug supply
- EDC system – data capture – Medidata Rave
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database
- Electronic Clinical Outcome Assessment (eCOA) system – electronic patient diary and patient reported outcomes

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

The study monitor and/or designee will visit each site prior to enrollment of the first patient, and periodically during the study. This study will use the principles of risk-based monitoring (ICH). This means that the monitoring strategy for any given site may vary based on site risk indicators. The investigator must allow study-related monitoring.

The study monitors will perform ongoing source data review to verify that data recorded in the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and eCRF data are timely, accurate and complete.

The investigator must keep all source documents on file with the eCRF. Case report forms and source documents must be available at all times for inspection by authorized representatives of the Sponsor and regulatory authorities.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (eCRFs) within the EDC system by trained site personnel. All required eCRFs must be completed for each and every patient enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor in the eCRFs. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient eCRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the Sponsor and regulatory authorities.

Corrections to the eCRF will be entered in the eCRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

12.3. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the Sponsor regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the Sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the Sponsor’s participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the Sponsor immediately
- Taking all appropriate measures requested by the Sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, eCRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the Sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final eCRF that will be provided to the Sponsor.

12.4.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of eCRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the Sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the Sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the Sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

An informed consent form (ICF) can be defined as either a paper consent form or an electronically-delivered consent (eConsent). An eConsent may be provided only where allowable by local laws and regulations and by site policies.

Due to disease severity, quarantine restrictions and/or other reasons related to COVID-19, it may be necessary to implement temporary or alternative measures to obtain informed consent per procedures outlined in the investigator site file.

The ICF used by the investigator must be reviewed and approved by the Sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF and documentation of approval must be provided to the Sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, or if there are significant changes to the study procedures, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

13.3. Patient Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number only, on eCRFs or other documents submitted to the Sponsor. Documents that will not be submitted to the Sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the Sponsor database, will be treated in compliance with all applicable laws and regulations. The Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patient, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the Sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

14. PROTOCOL AMENDMENTS

The Sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

The Sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the Sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Closeout of a Site

The Sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the Sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the Sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The Sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

19. REFERENCES

Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. Jama 2020; 323(16):1612-4.

Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med 2020; 382(19):1787-99.

CDC. Outpatient and Ambulatory Care Settings: Responding to Community Transmission of COVID-19 in the United States. https://www.cdc.gov/coronavirus/2019-ncov/hcp/ambulatory-care-settings.html. Published 2020a. Updated Accessed 27 April 2020.

CDC. Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 — United States, February 12–March 28, 2020. Morbidity and Mortality Weekly Report 2020b; 69(13).

CDC. Prevalence of Obesity Among Adults, by Household Income and Education — United States, 2011–2014. Morbidity and Mortality Weekly Report 2017; 66(50).

CDC. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) — United States, February 12–March 16, 2020. Morbidity and Mortality Weekly Report 2020c; 69(12).

Chen L, Liu HG, Liu W, Liu J, Liu K, Shang J, et al. [Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia]. Zhonghua Jie He He Hu Xi Za Zhi 2020a; 43(0):E005.

Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020b; 395(10223):507-13.

Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol 2019; 17(3):181-92.

Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol 2015; 1282(1-23.

Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020.

Han Y, Zhang H, Mu S, Wei W, Jin C, Xue Y, et al. Lactate dehydrogenase, a Risk Factor of Severe COVID-19 Patients. medRxiv 2020:2020.03.24.20040162.

He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med 2020; 26(5):672-5.

Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020; 181(2):271-80.e8.

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395(10223):497-506.

Jiang S, Hillyer C, Du L. Neutralizing Antibodies against SARS-CoV-2 and Other Human Coronaviruses. Trends Immunol 2020.

Li F. Structure, Function, and Evolution of Coronavirus Spike Proteins. Annu Rev Virol 2016; 3(1):237-61.

Lighter J, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, et al. Obesity in patients younger than 60 years is a risk factor for Covid-19 hospital admission. Clin Infect Dis 2020.

Liu Y, Yan LM, Wan L, Xiang TX, Le A, Liu JM, et al. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect Dis 2020.

Luo X, Zhou W, Yan X, Guo T, Wang B, Xia H, et al. Prognostic value of C-reactive protein in patients with COVID-19. medRxiv 2020:2020.03.21.20040360.

Magyarics Z, Leslie F, Bartko J, Rouha H, Luperchio S, Schörgenhofer C, et al. Randomized, Double-Blind, Placebo-Controlled, Single-Ascending-Dose Study of the Penetration of a Monoclonal Antibody Combination (ASN100) Targeting Staphylococcus aureus Cytotoxins in the Lung Epithelial Lining Fluid of Healthy Volunteers. Antimicrob Agents Chemother 2019; 63(8).

Ou X, Liu Y, Lei X, Li P, Mi D, Ren L, et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat Commun 2020; 11(1):1620.

Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020.

Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020:1-3.

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Ann Emerg Med 2006; 47(4):373-80.

Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. Jama 2020.

Song F, Shi N, Shan F, Zhang Z, Shen J, Lu H, et al. Emerging 2019 Novel Coronavirus (2019-nCoV) Pneumonia. Radiology 2020; 295(1):210-7.

Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell 2020; 181(2):281-92.e6.

Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. Jama 2020a; 323(11):1061-9.

Wang L. C-reactive protein levels in the early stage of COVID-19. Med Mal Infect 2020b.

Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020c; 395(10236):1569-78.

WHO. Coronavirus Disease 2019 (COVID-19) Situation Report – 90. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/. Published 2020a. Updated Accessed 20 April 2020.

WHO. Novel Coronavirus (2019-nCoV) Situation Report – 22. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/. Published 2020b. Updated Accessed 24 April 2020.

Wu C, Zheng S, Chen Y, Zheng M. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCoV, in the nasal tissue. medRxiv 2020a:2020.02.11.20022228.

Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. Jama 2020b.

Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020; 12(1):8.

Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. Jama 2020; 323(15):1488-94.

Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov. bioRxiv 2020:2020.01.26.919985.

Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395(10229):1054-62.

Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020; 382(8):727-33.

20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol, "A Master Protocol Assessing the Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Patients with COVID-19", and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the Sponsor or a partnership in which the Sponsor is involved. I will immediately disclose it in writing to the Sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the Sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the planned conduct of the study.

Study Title: A Master Protocol Assessing the Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Patients with COVID-19

Protocol Number: R10933-10987-COV-2067

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00112977 v1.0

ESig Approval	[redacted]
ESig Approval	[redacted]
ESig Approval	[redacted]
ESig Approval	[redacted]

Signature Page for VV-RIM-00112977 v1.0 Approved

Clinical Study Protocol

A MASTER PROTOCOL ASSESSING THE SAFETY, TOLERABILITY, AND EFFICACY OF ANTI-SPIKE (S) SARS-COV-2 MONOCLONAL ANTIBODIES FOR THE TREATMENT OF AMBULATORY PATIENTS WITH COVID-19

Compound:	REGN10933+REGN10987
Clinical Phase:	1/2/3
Protocol Number:	R10933-10987-COV-2067
Protocol Version:	Amendment 8
Amendment 8 Date of Issue	*See appended electronic signature page*
Amendment 7 Date of Issue	18 Dec 2020
Amendment 6 Date of Issue	14 Nov 2020
Amendment 5 Date of Issue	08 Aug 2020
Amendment 4 Date of Issue	11 Jul 2020
Amendment 3 Date of Issue	04 Jul 2020
Amendment 2 Date of Issue	19 June 2020
Amendment 1 Date of Issue	03 June 2020
Original Date of Issue:	29 May 2020

Medical/Study Director:

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[redacted], Early Clinical Development and Experimental Sciences

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AMENDMENT HISTORY

Amendment 8

The primary purpose of this amendment is to 1) end randomization to placebo in all phase 3 cohorts, and 2) revise the statistical analysis for cohort 1, including the primary endpoint, key secondary endpoints, hierarchical testing, and plan for interim/final analyses.

Description of Change	Brief Rationale	Section(s)
Phase 3 Randomization		
As of 25 February 2021, patients will no longer be randomized to placebo	Per IDMC recommendation	Table 1 Summary of Main Phase 3 Adaptations Section 6.1.3 Phase 3 Section 8.6 Method of Treatment Assignment
Phase 3 Statistical Analysis		
The following summarizes the planned statistical analysis for phase 3 cohort 1: • The primary endpoint will be proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 • The key secondary endpoints will be proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 to through day 29, and time to COVID-19 symptoms resolution. Symptoms will include a subset of those captured in the SE-C19, as described in the main text • The full analysis set (FAS) includes all randomized patients with COVID-19 symptoms (starting from the 800th symptomatic patient randomized in the study overall), regardless of whether they have risk factors for severe COVID-19 • The modified full analysis set (mFAS) includes all patients in the FAS with detectable SARS-CoV-2 RNA by RT-qPCR in nasopharyngeal swabs at randomization **and** ≥1 risk factor for severe COVID-19. The mFAS will be used to analyze the primary and key secondary endpoints • Concurrent with the final analysis of the primary endpoint for the 2400 mg treatment group, an interim analysis will be conducted on the primary endpoint for the 1200 mg treatment group • A hierarchy is provided for the primary and key secondary endpoints to control for multiplicity, including a Gamma family spending function to control for alpha in the interim and final analyses • Other endpoints, including those assessing emergency room (ER) visits and other medically-attended visits (MAVs), will be evaluated descriptively • Additional minor details were updated for consistency with the planned analysis Details of the revised statistical analysis are provided in the main text.	Primary endpoint changed based on health authority feedback. Other changes implemented to ensure that efficacy assessment of REGN10933 + REGN10987 is conducted with the most clinically-relevant endpoints	Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Section 3.2.1.5 Rationale for Phase 3 Adaptations Table 1 Summary of Main Phase 3 Adaptations Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints Figure 3 Study Flow Diagram, Phase 2 (and Phase 3 Prior to Amendment 6) Figure 4 Study Flow Diagram, Phase 3 (Cohort 1 Patients; Cohort 3 Patients ≥18 Years) Figure 5 Study Flow Diagram, Phase 3 (Cohort 2 Patients; Cohort 3 Patients <18 Years) Section 6.3 Planned Interim Analysis Section 11.1 Statistical Hypothesis Section 11.2 Justification of Sample Size Table 9 Estimated Sample Sizes at Each Analysis Time Point for Phase 3 Patients with ≥1 Risk Factor for Severe COVID-19 Section 11.3.1 Efficacy Analysis Sets Section 11.4.1 Patient Disposition Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis Section 11.4.4 Control of Multiplicity Table 11 Statistical Testing Hierarchy, Phase 3 Cohort 1 Analysis

Description of Change	Brief Rationale	Section(s)
		Table 12 Statistical Testing Hierarchy, Phase 3 Cohort 1 Analysis Section 11.5 Interim Analysis
The full analysis set (FAS) and modified full analysis set (mFAS) will not require that patients be randomized **and treated**; patients who are randomized and not treated will also be considered part of the FAS or mFAS.	Per health authority feedback	Section 11.3.1 Efficacy Analysis Sets
Additional details have been provided to describe the SE-C19 instrument.	To provide additional information related to a key secondary endpoint	Section 9.2.13 Exploratory Patient-Reported Symptoms Table 7 Symptoms Evaluated in the SE-C19 [new]
Clarified that, in total, up to approximately 8500 patients will be enrolled in phase 3 cohort 1.	To ensure an accurate description of planned enrollment	Table 1 Summary of Main Phase 3 Adaptations Section 7.1 Number of Patients Planned
Added an exploratory objective to assess the clinical efficacy of different dose levels of REGN10933 + REGN10987, as measured by COVID-19-related hospitalizations or all-cause death.	To better understand potential differences in clinical efficacy between REGN10933 + REGN10987 dose levels	Section 2.3 Exploratory Objectives
Time to COVID-19 symptoms resolution will be evaluated as an exploratory endpoint in phase 3 cohort 2.	To assess the potential impact of REGN10933 + REGN10987 on COVID-19 symptoms	Section 4.3 Exploratory Endpoints
Safety Assessment		
For patients who are <12 years of age, a phone call will be made within 6 to 8 hours after completing the infusion to collect targeted safety information. A phone call on day 2 is not required. These patients (or their caregivers) should continue to be instructed to contact the site within the first 24 hours post-infusion if they experience any side effects. This change is consistent with a memorandum that was previously provided to study sites.	Per health authority feedback; to ensure appropriate post-infusion monitoring for younger patients <12 years old	Section 6.1.3 Phase 3 Section 9.1.1 Footnotes for the Schedule of Events Tables, #17
Clarified that any SAE resulting in death that occurs prior to study day 169 should be reported, regardless of patient withdrawal or early termination.	To ensure appropriate capturing of vital status	Section 10.1.1 General Guidelines
Other Changes and Clarifications		
For all study phases, the viral sequencing exploratory endpoint has been removed. The exploratory objective has been revised to the following: • To evaluate viral variants at baseline and post-treatment In addition, clarified that the results of viral sequencing will be reported separately from the CSR.	To provide flexibility with respect to planned viral sequencing analyses	Section 2.3 Exploratory Objectives Section 9.2.10.3 Virology
Added exploratory objective for phase 3 cohort 3: • To describe clinical outcomes of patients treated with REGN10933+REGN10987 using various measures of COVID-19-related medically-attended visits or all-cause death	To assess clinical outcomes among patients who are pregnant at randomization	Section 2.3 Exploratory Objectives

Description of Change	Brief Rationale	Section(s)
Clarified that cohort 2 and cohort 3 may continue to enroll after enrollment of cohort 1 has been completed.	To clarify flexibility of enrollment in phase 3 cohorts	Table 1 Summary of Main Phase 3 Adaptations Section 11.2 Justification of Sample Size
In cohort 2, there will be a minimum enrollment of 20 patients <10 kg (10 per treatment group) and 20 patients between ≥10 kg and <40 kg.	Per health authority feedback	Table 1 Summary of Main Phase 3 Adaptations Section 11.2 Justification of Sample Size
The following phase 3 operational clarifications or changes have been made: • Study visits (including phone calls) are not required solely to collect continuously-monitored assessments, if no other assessments are planned on that day. • Study visits are not required on days when only electronic survey data are collected • TEAEs that led to a medically-attended visit will be collected starting on day 1 post-infusion, when applicable (day 1 post dose collection was previously missing from the schedule of events) • In phase 3 cohort 2, vital status was incorrectly marked as a screening assessment. This error has been corrected • On days 60 and 90, the window for EQ-5D-5L (and EQ-5D-Y) assessment is ±3 days. On days 120 and 169, the window is ±7 days	To ensure operational clarity, including avoiding unnecessary study visits and ensuring appropriate capturing of relevant adverse events and concomitant procedures	Section 8.10 Concomitant Medications and Procedures Table 5 Schedule of Events: Phase 3 (Cohort 1 Patients; Cohort 3 Patients ≥18 Years) Table 6 Schedule of Events: Phase 3 (Cohort 2 Patients; Cohort 3 Patients <18 Years) Section 9.1.1 Footnotes for the Schedule of Events Tables, #7, 8, 14
The following changes to concomitant medication recording have been made: • In addition to targeted concomitant medication, concomitant procedures will also be recorded when applicable • In addition to the listed targeted concomitant medications, “any other vaccines” and “oxygen” will also be recorded as applicable	To capture additional clinical information	Section 9.2.4.3 Record Targeted Concomitant Medications and Concomitant Procedures
The following clarification has been made with respect to medically-attended visits related to COVID-19: • During each indicated collection visit (as provided in the schedule of events), all previously unrecorded COVID-19-related medically-attended visits and details will be recorded, beginning from the day of dosing up to and including the day of collection	To ensure appropriate capturing of clinically-relevant information	Section 9.2.3.2 COVID-19-Related Medically-Attended Visit Details
Clarified that cohort 2 **and cohort 3** will only be enrolled where permitted by local requirements.	To provide enrollment flexibility per regional requirements	Table 1 Summary of Main Phase 3 Adaptations Section 7.2.1 Inclusion Criteria, #1
Clarified that in addition to WPAI+CIQ, EQ-5D-5L, and EQ-5D-Y-5L, the return to usual health and return to usual activities surveys will only be administered at sites when regionally available.	To provide operational flexibility	Section 9.1.1 Footnotes for the Schedule of Events Tables, #14
Neutralizing antibody (NAb) analyses will be conducted in phase 2 and phase 3 (all cohorts).	To provide additional assessment of potential for neutralizing antibodies against	Section 4.2 Secondary Endpoints

Description of Change	Brief Rationale	Section(s)
	REGN10933 + REGN10987	
Clarified that assessment of immunogenicity will be a secondary objective for cohort 2 and cohort 3 of phase 3, and that assessment of drug concentration will be a secondary objective for cohort 3 of phase 3; the objectives were previously listed incorrectly as primary objectives.	To ensure accurate descriptions of planned analyses	Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Table 1 Summary of Main Phase 3 Adaptations Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints
The risk-benefit section has been updated to reflect the current Investigator's Brochure (edition 5). This includes the addition of hypersensitivity reactions (including infusion-related reactions and injection site reactions) as an important identified risk. Additional contextual information related to COVID-19 vaccination as a theoretical consideration has also been provided.	To provide current information regarding the potential risks and benefits of REGN10933 + REGN10987	Section 3.3 Risk-Benefit
In light of the increasing number of therapeutic and preventative COVID-19 agents approved or conditionally authorized reference to individual agents has been removed. References to FDA and EMA have been provided as a general resource for currently-available agents.	To ensure current, accurate, and consistent information	Section 1.6 Current Landscape of Therapeutic and Preventative Agents for COVID-19 [deleted] Section 1.6 A Randomized, Placebo-Controlled Study of Anti-SARS-CoV-2 S Protein Monoclonal Antibodies in Ambulatory Patients with COVID-19
Updates to background information, minor clarifications for consistency, and other minor updates (typographical, editorial) were made.	To ensure clarity, accuracy, and consistency	Throughout the document

Amendment 7

The primary purpose of this amendment is to modify the phase 3 portion of the study in response to health authority feedback. Related modifications (eg, with respect to patients who are pregnant) and other clarifications have also been implemented.

Description of Change	Brief Rationale	Section(s)
All-cause death was added to the cohort 1 (≥18 years) primary endpoint (ie, COVID-19-related medically-attended visits **or all-cause death**) and to several secondary endpoints in cohort 1 and cohort 2 (<18 years). The phase 3 sample size was not updated as a result of this change.	Per health authority feedback; to capture an additional event of clinical importance	Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Section 3.2.1.5 Rationale for Phase 3 Adaptations Table 1 Summary of Main Phase 3 Adaptations Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints Section 11.1 Statistical Hypothesis Section 11.2 Justification of Sample Size Section 11.4.3.1 Primary Efficacy Analysis
In cohort 1, additional secondary endpoints were designated as key endpoints, and the statistical hierarchy was updated to control for multiplicity.	To ensure rigorous statistical analysis	Section 4.2 Secondary Endpoints Section 11.4.3.2 Secondary Efficacy Analysis Section 11.4.4 Control for Multiplicity
Patients who are pregnant at randomization, regardless of age, will be enrolled in a separate double-blinded cohort (cohort 3): • Cohort will be randomized 1:1 to REGN10933+REGN1087 1200 mg or 2400 mg, tiered as applicable based on weight • Patients in the cohort will not be randomized to placebo • Randomization will not be stratified • Depending on their age, patients in cohort 3 will follow the cohort 1 (≥18 years) or cohort 2 (<18 years) schedule of events • For patients in cohort 3 who are ≥18 years, additional samples will be collected for drug concentration and immunogenicity assessment • Analysis will be descriptive and will focus on safety and PK	To increase collection of safety and PK information related to REGN10933 + REGN10987 among patients who are pregnant	Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Table 1 Summary of Main Phase 3 Adaptations Section 7.2.1 Inclusion Criteria, #9 Section 9.1.1 Footnotes for the Schedule of Events Tables, #12, 15
The following changes will be made to cohort 2 (and patients <18 years in cohort 3): • Enrollment will be limited to patients who are symptomatic at randomization and have ≥1 risk factor for severe COVID-19 (ie, enrollment is discontinued for asymptomatic patients) • Removed the presence/absence of COVID-19 symptoms as a stratification factor for randomization • Increased the frequency of vital signs assessments performed during and after infusion for patients <12 years old • For patients who are <12 years old, an additional phone call will be made on day 2 (within 24 hours of	Per health authority request; to focus enrollment on patients with highest potential benefit and ensure appropriate safety monitoring during and within 24 hours after study drug administration	Section 3.2.1 Rationale for Study Design Section 3.2.1.5 Rationale for Phase 3 Adaptations Table 1 Summary of Main Phase 3 Adaptations Section 6.1 Study Description and Duration Section 7.1 Number of Patients Planned Section 7.2.1 Inclusion Criteria, #4, 9

Description of Change	Brief Rationale	Section(s)
infusion) for collection of targeted safety information, and these patients (or their caregivers) should be instructed to contact the site within the first 24 hours post-infusion if they experience any side effects. • Clarified that a minimum of 6 patients <10 kg and 6 patients between ≥10 kg and <40 kg will be enrolled		Section 8.6 Method of Treatment Assignment Section 11.2 Justification of Sample Size Section 6.1.3 Phase 3 Figure 5 Study Flow Diagram, Phase 3 (Cohort 2) Section 9.1.1 Footnotes for the Schedule of Events Tables, #6, #17 Table 6 Schedule of Events: Phase 3 (Cohort 2)
In addition to what is currently being collected, the following safety information will be collected in all phase 3 cohorts: • All treatment-emergent adverse events that led to a medically-attended visit (hospitalization, emergency room visit, urgent care visit, physician's office visit, or telemedicine visit), regardless of relatedness to COVID-19, through day 29 • All treatment-emergent serious adverse events and deaths, from day 30 to day 169 • In addition to standard collection of pregnancy outcome information, for newborn infants of patients who were treated in the study and were pregnant at randomization or became pregnant at any time in the study, the incidence and outcome of any SARS-CoV-2 infection will be collected during day 120 and day 169 follow-up phone calls and reported in the pregnancy report form	Per health authority request and for more comprehensive analysis of medically attended visits and the safety profile of REGN10933 + REGN10987	Section 3.2.1 Rationale for Study Design Section 3.2.1.5 Rationale for Phase 3 Adaptations Section 5.3 Safety Variables Section 6.1.3 Phase 3 Table 5 Schedule of Events: Phase 3 (Cohort 1) Table 6 Schedule of Events: Phase 3 (Cohort 2) Section 9.1.1 Footnotes for the Schedule of Events Tables, #7, 16 Section 9.2.4.2 Adverse Event Monitoring Section 9.2.5 Post-Day 29 Follow-up by Phone Section 10.1.1 General Guidelines Section 10.1.3 Events that Require Expedited Reporting to Sponsor
Clarified that viral variants suspected to confer decreased susceptibility to REGN10933 and/or REGN10987 will be evaluated in nonclinical work separate from this protocol.	Per health authority request	Section 9.2.10.3 Virology
Eligibility criteria have been modified to allow planned use of any authorized or approved vaccine for SARS-CoV-2, if (at the time of screening) it is planned **after** 90 days following study drug administration. This screening allowance may be modified as applicable if CDC recommendations change. • Prior use (prior to randomization), current use (at randomization), or planned use (within 90 days of study drug administration or per current CDC recommendations, as applicable) of any authorized or approved vaccine for SARS-CoV-2 is excluded • Prior, current, or future plans to participate in a clinical research study of an investigational vaccine for SARS-CoV-2 is also excluded	Per current CDC recommendations (CDC, 2020a)	Section 7.2.2 Exclusion Criteria, #13, 14
The followings clarifications were made with respect to assessment of women of childbearing potential (WOCBP) and women who are pregnant: • Pregnancy testing at screening must be performed in all WOCBP, regardless of pregnancy status	To ensure accurate information is collected regarding pregnancy	Section 9.2.1.4 Medical History Section 9.2.6 Pregnancy Test for Women of Childbearing Potential Section 10.1.3 Events that Required Expedited Reporting to the Sponsor

Description of Change	Brief Rationale	Section(s)
• Pregnancy or breastfeeding status at screening must be collected as medical history, if applicable • A paper pregnancy report form must be completed for each patient who becomes pregnant or is pregnant at the signing of consent		
Definitions of risk factors for severe COVID-19 were changed as follows: • Cohort 1: clarified that body mass index (BMI) greater than or equal to 30 (not greater than 30) constitutes a risk factor for severe COVID-19 • Cohort 1: clarified that age greater than **or equal to** 50 years constitutes a risk factor for severe COVID-19 • Cohort 2: for patients at least 2 years old, BMI ≥95th percentile for age and sex, based on CDC growth charts, will constitute a risk factor • Cohort 2: added a new risk factor for severe COVID-19 as an inclusion criterion: Any underlying genetic, neurologic, or metabolic condition, or congenital heart disease deemed by the investigator to constitute a risk factor for severe COVID-19 (note that immunocompromised/on immunosuppressive treatment is already considered a risk factor and is accounted for separately)	To clarify risk factors for severe COVID-19 and ensure alignment with CDC guidance, where applicable	Section 3.2.1.5 Rationale for Phase 3 Adaptations Section 7.2.1 Inclusion Criteria, #9
Updated concomitant medications list such that any medication used to treat an adverse event will be recorded	To ensure collection of clinically relevant concomitant medications	Section 9.2.4.3 Record Targeted Concomitant Medications
Clarified that for the screening SARS-CoV-2 diagnostic test, the **sample** must be collected ≤72 hours of randomization. Samples are not valid for screening if collected >72 hours from randomization, even if the test is performed, or results reported, within the 72-hour window.	To ensure appropriate screening for SARS-CoV-2 infection	Section 7.2.1 Inclusion Criteria
Removed language stating that if diagnostic SARS-CoV-2 testing was performed outside of the allowed window, a new test is required for study inclusion. Language was retained in error. Per study exclusion criteria, patients will be excluded if they have a positive SARS-CoV-2 antigen or molecular diagnostic test from a sample collected >72 hours prior to randomization	To ensure accurate information	Section 9.2.1.2 Diagnostic Test for SARS-CoV-2
Provided example of monoclonal antibody (bamlanivimab) that is considered exclusionary for study enrollment	For clarity	Section 7.2.2 Exclusion Criteria, #2, 3
Members of the clinical site study team and their immediate family members are now excluded from enrolling in the study	To ensure integrity of study data and analysis	Section 7.2.2 Exclusion Criteria, #14
In cohort 1, the following blood samples will no longer be collected: • Serum for cytokines and CK-MB • Plasma for hsTroponin Note that the descriptions of exploratory biomarker, analyses, as well as exploratory patient-reported symptom analyses conducted during prior study phases or time periods have been retained in protocol for historical purposes.	To reduce burden of blood sample collections	Table 5 Schedule of Events: Phase 3 (Cohort 1) Section 9.2.10 Exploratory Pharmacodynamic/Biomarker Analyses Section 9.2.13 Exploratory Patient-Reported Symptoms

Description of Change	Brief Rationale	Section(s)
Blood chemistry samples that are collected will not be analyzed for ferritin.	To reduce sample analyses with less relevant clinical significance	Table 5 Schedule of Events: Phase 3 (Cohort 1) Table 6 Schedule of Events: Phase 3 (Cohort 2) Section 9.2.7 Laboratory Testing
Columns have been added to explicitly indicate collection of EQ-5D-5L and EQ-5D-Y-5L at day 60 and day 90. This was previously indicated by a footnote in the schedule of events.	To improve schedule clarity	Section 9.1.1 Footnotes for the Schedule of Events Tables, #14
WPAI+CIQ, EQ-5D-5L, and EQ-5D-Y-5L will only be administered at sites when regionally available.	To provide operational flexibility	Section 9.1.1 Footnotes for the Schedule of Events Tables, #14
Added that an interim analysis of phase 3 cohort 2 may be conducted for regulatory purposes when the phase 3 cohort 1 primary analysis is performed.	To provide more details for the phase 3 statistical analysis plan	Section 11.5 Interim Analysis
Removed incorrectly marked medical history assessment on day 7.	To ensure accuracy	Table 6 Schedule of Events: Phase 3 (Cohort 2)
Removed and/or simplified schedule of events footnotes that contained information relevant to phase 1 and phase 2, which are now closed.	To simplify interpretation of phase 3 schedule of events	Section 9.1.1 Footnotes for the Schedule of Events Tables, #2, 3, 4, 6, 7, 9, 11, 12, 14, 15
Clarified that **approximately** 600 patients will be enrolled in the PK sub-study	To ensure accuracy	Section 9.2.8 Drug Concentration Measurements and Samples
Updated phase 1 endpoint to align with phase 1/2 statistical analysis plan.	To ensure accurate description of statistical analysis that was performed	Section 4.1 Primary Endpoints
Updates to background information and other minor updates were made.	To ensure current, accurate, and consistent information	Throughout the document

Amendment 6

The purpose of this amendment is to adapt the phase 3 portion of the study based on data from phase 1 and phase 2. Major adaptations include changes to the patient population, treatment arms, objectives/endpoints, and sample size.

The following table outlines all changes made to the protocol and the affected sections.

Description of Change	Brief Rationale	Section(s)
Patient Eligibility (Major Phase 3 Adaptation)		
• Females who are pregnant or breastfeeding can enroll in the study • Patients from 0 to <18 years will be enrolled as a separate cohort (cohort 2), where permitted by local requirements. Patients ≥18 years of age will be enrolled in cohort 1 • Patients in cohort 1 must have ≥1 risk factor for severe COVID-19. Patients in cohort 2 must have ≥1 risk factor for severe COVID-19 or live with a housemate who has ≥1 risk factor for severe COVID-19	To adapt the phase 3 portion of the study based on phase 2 data and to evaluate REGN10933 + REGN10987 in younger patients and pregnant/breastfeeding women with COVID-19	Section 3.2.1.5 Rationale for Phase 3 Adaptations [new] Section 5.1 Demographic and Baseline Characteristics Section 6.1 Study Description and Duration Section 7.2.1 Inclusion Criteria, #1, 2, 9 Section 7.2.2 Exclusion Criteria, #10, 11, 12

Description of Change	Brief Rationale	Section(s)
• Patients with a known positive SARS-CoV-2 serology test will be excluded • Patients with a positive SARS-CoV-2 antigen test or molecular diagnostic test from a sample collected >72 hours prior to randomization will be excluded • Patients with active infection with influenza or other non-SARS-CoV-2 respiratory pathogen, confirmed by a diagnostic test, will be excluded *Note: A subset of patients in phase 3 were enrolled prior to the phase 3 adaptations implemented in protocol amendment 6. These patients will not be consented to protocol amendment 6 and will continue to follow the protocol schedule to which they were last consented.*		Section 9.2.5 Post-Day 29 Follow-up by Phone Section 9.2.6 Pregnancy Test for Women of Childbearing Potential Section 10.1.3 Events That Require Expedited Reporting to Sponsor Section 11.4.1 Patient Disposition Section 13.2 Informed Consent
Treatment Arms (Major Phase 3 Adaptation)		
• For cohort 1, the REGN10933+REGN10987 8000 mg IV treatment arm will be dropped. The REGN10933 + REGN10987 2400 mg IV treatment arm and placebo arm will be retained. A new treatment arm will be added to assess REGN10933+REGN10987 1200 mg IV • For cohort 2, the highest dose tested will be REGN10933 + REGN10987 2400 mg IV. Weight-tiered dosing will be used in this cohort	To adapt the phase 3 portion of the study based on phase 2 data	Section 3.2.1.2 Adaptive Master Protocol Design Section 3.2.1.5 Rationale for Phase 3 Adaptations [new] Section 3.2.2 Rationale for Dose Selection Section 6.1.3 Phase 3 [new] Section 8.1 Investigational and Reference Treatments Section 8.6 Method of Treatment Assignments
Objectives/Endpoints (Major Phase 3 Adaptation)		
• For cohort 1, the primary endpoint will be COVID-19-related medically-attended visits (MAVs). Key pre-specified secondary endpoints include various types of COVID-19-related MAVs and related outcomes • For cohort 2, the primary endpoints will be safety/tolerability and drug concentrations in serum over time • For cohort 2, secondary analyses will be descriptive • Virologic analyses for both cohorts will be secondary and descriptive • [redacted]	To adapt the phase 3 portion of the study based on phase 2 data	Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Section 2.3 Exploratory Objectives Section 3.2.1.5 Rationale for Phase 3 Adaptations [new] Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints Section 6.1.3 Phase 3 [new] Table 5 Schedule of Events: Phase 3 (Cohort 1) [new] Table 6 Schedule of Events: Phase 3 (Cohort 2) [new] Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1, Phase 2, and Phase 3), footnote #4 [redacted]

Description of Change	Brief Rationale	Section(s)
Sample Size (Major Phase 3 Adaptation)		
• Enrollment in phase 3 cohort 1 is anticipated to be approximately 5400 patients • Phase 3 cohort 1 will continue until at least 80 hospitalizations or ER visits are observed in patients enrolled under protocol amendment 6 (or subsequent amendment) into the primary analysis population (patients in modified full analysis set [mFAS] with at least 1 risk factor) ***and*** the total number of hospitalizations or ER visits during the study in the primary analysis population is more than 120 • Phase 3 cohort 2 will enroll up to approximately 180 patients	To adapt the phase 3 portion of the study based on phase 2 data	Section 3.2.1.5 Rationale for Phase 3 Adaptations [new] Section 7.1 Number of Patients Planned Section 11.2 Justification of Sample Size
Other Phase 3 Adaptations		
Phase 3 cohort 1 schedule of events will be adapted to include the following major changes from phase 2: • Patients will be followed up by phone on days 120 and 169 (end of study) for assessments including vital status • Virologic assessments will be more limited in scope. Nasopharyngeal (NP) swabs will only be collected on days 1, 7, 15, and 29 • For targeted safety information, treatment-emergent serious adverse events (SAEs), if determined by the investigator to be related to study drug, will be recorded from day 30 to day 169 • A subset of patients will be enrolled in a PK sub-study at selected participating sites. *Note: A subset of patients in phase 3 were enrolled prior to the phase 3 adaptations implemented in protocol amendment 6. These patients will not be consented to protocol amendment 6 and will continue to follow the protocol schedule to which they were last consented.*	Per health authority feedback, and to adapt the phase 3 study design based on phase 2 data	Section 6.1 Study Description and Duration Section 6.1.3 Phase 3 [new] Figure 4 Study Flow Diagram, Phase 3 (Cohort 1) [new] Figure 5 Study Flow Diagram, Phase 3 (Cohort 2) [new] Section 9.2.5 Post-Day 29 Follow-up by Phone Table 5 Schedule of Events: Phase 3 (Cohort 1) [new] Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1, Phase 2, and Phase 3), footnotes #7, 11, 12, 13, 14, 15 Section 9.2.8 Drug Concentration Measurements and Samples Section 10.1.1 General Guidelines Section 10.1.2 Reporting Procedure
Phase 3 cohort 2 will follow similar schedule of events as cohort 1, with key exceptions as follows: • Blood sample collection schedules for laboratory and biomarker analyses will vary according to body weight • Additional NP swab sample will be collected on day 3 • Blood sample collection schedules for pharmacokinetics and immunogenicity will utilize sparse sampling and vary based on randomly assigned sampling schedules • Limited biomarker samples will be collected • Patient-reported electronic surveys/questionnaires will only be collected in patients ≥12 years • Treatment-emergent grade ≥3 AEs will be collected through day 29	To ensure appropriate assessment of safety and efficacy of REGN10933 + REGN10987 and to adjust blood volumes appropriately for younger pediatric patients	Section 6.1.3 Phase 3 [new] 4 Study Flow Diagram, Phase 3 (Cohort 1) [new] Figure 5 Study Flow Diagram, Phase 3 (Cohort 2) [new] Section 7.2.1 Inclusion Criteria, #1a Section 8.1 Investigational and Reference Treatments Section 8.6 Method of Treatment Assignment Table 6 Schedule of Events: Phase 3 (Cohort 2) [new] Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1, Phase 2, and Phase 3), footnotes #7, 11, 13, 14, 15

Description of Change	Brief Rationale	Section(s)
		Section 9.2.5 Post-Day 29 Follow-up by Phone Section 9.2.9 Immunogenicity Measurements and Samples
Details of COVID-19-related medically-attended visits were revised.	To ensure appropriate assessment of the clinical efficacy of REGN10933 + REGN10987	Section 9.2.3.2 COVID-19-Related Medically-Attended Visit Details
Risk factors for hospitalization due to COVID-19 were removed as a stratification factor for randomization. Patients in both cohorts will be stratified by country, and (in cohort 2 only) by the presence or absence of COVID-19 symptoms.	Both cohorts in phase 3 will have ≥1 risk factor for severe COVID-19	Section 8.6 Method of Treatment Assignments
Immunogenicity will be assessed by anti-drug antibodies (ADA) and neutralizing antibody (NAb) analyses, as a secondary endpoint in cohort 1 and a primary endpoint in cohort 2.	To ensure comprehensive assessment of potential immunogenic response following REGN10933 + REGN10987 administration	Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints Section 5.5 Immunogenicity Variables Section 9.2.9 Immunogenicity Measurements and Samples Section 11.3.4 Immunogenicity Analysis Sets Section 11.4.8 Analysis of Immunogenicity Data
Patient eligibility criteria were updated to: • Clarify the acceptable timing for a historical record of positive SARS-CoV-2 test result • Clarify informed consent requirements for cohort 2 patients • Add that patients must be able to understand and complete study-related questionnaires (cohort 1 and cohort 2 patients aged ≥12 years only) • Clarify that patients must not have been admitted to a hospital for COVID-19 prior to randomization, or hospitalized (inpatient) for any reason at randomization • Clarify exclusions related to prior, current, or planned COVID-19 treatments	To ensure appropriate enrollment and data analysis for phase 3 and to provide operational clarity and flexibility	Section 7.2.1 Inclusion Criteria, #2, 6, 8 Section 7.2.2 Exclusion Criteria, #1, 3; #8, 9 [removed]; #10, 11, 12, 13 [added]
For phase 3 cohort 1 efficacy analysis, the Sponsor may request the IDMC to perform 1 or more interim analyses for efficacy	To ensure appropriate assessment of potential efficacy signals	Section 11.5 Interim Analysis
Other Changes and Clarifications		
For patients in this study who are also index cases of household contacts in the R10933-10987-COV-2069 prophylaxis study, data from this study may be used as part of analyses on the COV-2069 study.	To assess the potential impact of REGN10933+REGN10987 treatment of an index case participating in this study on infection rates in household contacts participating in COV-2069.	Section 6.1.3 Phase 3

Description of Change	Brief Rationale	Section(s)
Prior to unblinding for interim analysis of phase 1/2 and analysis of phase 2, changes were made to the statistical analysis plan, including endpoints and analysis descriptions. These changes have been updated in the protocol	To ensure consistency and accuracy of the study statistical plans.	Section 3.2.1.3 Rationale for Phase 1 and Phase 2 Objectives Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints Section 6.3 Planned Interim Analysis Section 11.5 Interim Analysis
Emergency unblinding procedures were clarified, including manual unblinding in case of IWRS unavailability.	Per health authority request	Section 8.8 Emergency Unblinding
Baseline blood samples may be collected at either day -1 or day 1 (ie, screening or pre-dose) prior to randomization. For patients in phase 3 cohort 2.	To provide operational flexibility.	Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1, Phase 2, and Phase 3), #12
Study monitoring plan was updated to allow off-site/remote monitoring of study sites.	Per health authority request; to provide flexibility for site monitoring due to COVID-19.	Section 12.2.1 Monitoring of Study Sites
Risk-benefit language was updated.	To provide updated risk-benefit information for the program and considerations for a broader patient population	Section 3.3 Risk-Benefit
Descriptions of the statistical plan were updated as follows: • Statistical hypotheses and analysis set definitions were updated • Details regarding control of multiplicity were added • Phase 3 efficacy analysis methods were added • For phase 3, plans for interim analyses were added	To update descriptions of the statistical plan	Section 3.1 Hypotheses Section 6.3 Planned Interim Analysis Section 11 Statistical Plan Section 11.1 Statistical Hypotheses Section 11.3.1 Efficacy Analysis Sets Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis Section 11.4.4 Control of Multiplicity
Descriptions of viral sequencing parameters were updated to expand beyond analyses of potential viral resistance.	For accuracy	Section 9.2.10.3 Virology
Detailed descriptions of exploratory patient-reported symptoms were added.	To provide context for patient-reported symptom assessments	Section 9.2.13 Exploratory Patient-Reported Symptoms
REGN10989 monotherapy will no longer be considered as part of this adaptive master protocol. References to REGN10989 have correspondingly been removed throughout the protocol.	Based on preclinical viral resistance data showing viral escape following monotherapy with anti-SARS-CoV-2 monoclonal antibodies, this study to assess combination therapies and will no longer include monotherapy arms.	Throughout the document

Description of Change	Brief Rationale	Section(s)
References to phase 1 and phase 2 were removed from the study synopsis.	For operational clarity, since phase 1 and phase 2 are now closed	Clinical Study Protocol Synopsis
References to “low dose” and “high dose” were removed.	To ensure clarity with the addition of different dose levels in phase 3	Throughout the document
Updates to background information, administrative updates, and other minor updates to align with phase 3 adaptations were made.	To ensure current, accurate, and consistent information	Throughout the document

Amendment 5

Description of Change	Brief Rationale	Section(s)
Added new cohort of patients in phase 2 to evaluate asymptomatic patients with SARS-CoV-2 infection. Total planned enrollment for phase 2 has been increased to 1300 patients to accommodate this cohort.	To broaden patient eligibility and enable broader assessment of potential treatment impact on viral burden and other measures	Section 3.2.1.3 Rationale for Primary Objectives Section 3.2.1.5 Stratification According to Risk of Hospitalization Due to COVID-19 Section 6.1 Study Description and Duration Section 6.1.2 Phase 2 Figure 3 Study Flow Diagram, Phase 2 Section 7.1 Number of Patients Planned Section 7.2.1 Inclusion Criteria, #4 Section 8.6 Method of Treatment Assignment Section 11.2 Justification of Sample Size Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis
In phase 2, added new secondary clinical endpoint to assess development of symptoms consistent with COVID-19.	To assess the impact of treatment on the development of COVID-19 symptoms in patients who are initially asymptomatic with SARS-CoV-2 infection	Section 4.1 Secondary Endpoints
In phase 2, added new secondary clinical endpoint to assess duration of symptoms consistent with COVID-19.	To assess the impact of treatment on the duration of symptoms	Section 4.1 Secondary Endpoints
Removed screening requirement that patients have ≥1 of the following symptoms at randomization: fever, cough, shortness of breath.	To broaden patient eligibility and to facilitate assessment of potential treatment impact on other clinical manifestations of COVID-19	Section 7.2.1 Inclusion Criteria, #3 [deleted]
At screening, diagnostic testing for SARS-CoV-2 infection will allow antigen tests in addition to molecular tests.	To provide operational flexibility	Section 7.2.1 Inclusion Criteria, #3 Table 4 Schedule of Events: Phase 2 Section 9.2.1.2 Diagnostic Test for SARS-CoV-2
Revised exclusion criteria medications to exclude patients with prior, current, or planned future use of EUA-approved medications (eg, remdesivir), convalescent serum, IVIG, other anti-SARS-CoV2 antibodies, or systemic steroids, thereby allowing antecedent use of other COVID-19 investigational medications such as hydroxychloroquine and azithromycin. Clarified that excluded agents are permitted only if medically indicated.	To broaden patient eligibility	Figure 3 Study Flow Diagram, Phase 2 Section 7.2.2 Exclusion Criteria, #3 Section 7.2.2 Exclusion Criteria, #4 [consolidated with #3], #5, [deleted] Section 8.10.1 Prohibited and Permitted Medications

In phase 2, added blood samples for hematology, blood chemistry, and coagulation tests on days 7 and 15. In phase 2, added blood samples for cardiac biomarkers at baseline and on days 7, 15, and 29.	To enable more comprehensive analysis of safety and efficacy by including additional biomarkers of inflammation and cardiac and/or other organ injury	Section 5.6 Pharmacodynamic and Other Biomarker Variables Section 6.1.2 Phase 2 Table 4 Schedule of Events: Phase 2 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #10 Section 9.2.7 Laboratory Tests Section 9.2.10.8 Serum and Plasma for Cardiac Biomarkers [section added]
Removed post-dose collection of SE-C19 and PGIS and extended daily collection of SE-C19 and PGIS until day 29	To ensure that assessments are only captured once in each 24 hour period , and to provide additional information on patient-reported symptoms at later time points	Table 4 Schedule of Events: Phase 2
Minor clarifications were made to descriptions of other biomarker analyses.	To better describe planned analyses	Section 9.2.10.4 Serological Immunoassays for Anti-SARS-CoV-2 Antibodies Section 9.2.10.5 Serum and Plasma for Research Section 9.2.10.7 Cytokines
Clarified collection of medical history: COVID-19, if applicable, with start date as date of onset of first symptoms.	To ensure appropriate collection of symptom onset	Section 9.2.1.4 Medical History
Information regarding review of sentinel safety group (part A) was added.	To update safety information for the program	Section 3.2.1.1 Phase 1 Sentinel Safety Group
Updated phase 2 interim analysis plans.	To allow flexibility of interim analyses	Section 6.3 Planned Interim Analysis Section 11.4.4 Control of Multiplicity Section 11.5 Interim Analysis
Minor editorial updates made to reflect addition of asymptomatic cohort.	To ensure accuracy and consistency	Section 1.3 Outpatient Care as a Potential COVID-19 Treatment Setting Section 1.6 A Randomized, Placebo-Controlled Study of Anti-SARS-CoV-2 S Protein Monoclonal Antibodies in Ambulatory Patients with COVID-19 or Asymptomatic SARS-CoV-2 Infection Section 3.1 Hypotheses Section 3.2.1 Rationale for Study Design
Removed a duplicate secondary endpoint for phase 3; other minor editorial and administrative updates were made.	To ensure accuracy and consistency	Section 1.1 Emergence of SARS-CoV-2 and COVID-19 Section 4.1 Secondary Endpoints Section 8.6 Method of Treatment Assignment Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #4

Amendment 4

Description of Change	Brief Rationale	Section(s)
Nasal swabs and saliva samples will no longer be collected in phase 2 and are no longer planned for phase 3. Only nasopharyngeal (NP) swabs will be collected in phase 2 and phase 3.	To allow adequate assessment of virologic efficacy, as NP swab is the current gold standard to detect SARS-CoV-2	Clinical Study Protocol Synopsis: Objectives, Study Design, Endpoints, Procedures and Assessments Section 2.2 Secondary Objectives Section 4.1 Secondary Endpoints Section 6.1.2 Phase 2 Figure 2 Study Flow Diagram, Phase 1 Figure 3 Study Flow Diagram, Phase 2 Table 4 Schedule of Events: Phase 2 Section 9.2.3.1 Nasopharyngeal Swab, Nasal Swab, and Saliva Collection Section 11.4.3.2 Secondary Efficacy Analysis
Phase 2 sample size has been increased to enable additional enrollment.	To allow adequate assessment of virologic efficacy	Figure 3 Study Flow Diagram, Phase 2 Section 7.1 Number of Patients Planned Section 11.2 Justification of Sample Size
Interim analysis plan was updated to allow more flexibility in timing.	To allow flexibility of interim analyses	Section 6.3 Planned Interim Analysis Section 9.2.3.1 Nasopharyngeal Swab, Nasal Swab, and Saliva Collection Section 11.5 Interim Analysis
A modified full analysis set (mFAS) was added and includes all randomized patients with a positive RT-qPCR for SARS-CoV-2 in NP swab at randomization.	To allow adequate assessment of virologic efficacy	Section 11.3.1 Efficacy Analysis Sets Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis
An additional secondary virologic endpoint has been added.	To allow adequate assessment of virologic efficacy	Section 4.1 Secondary Endpoints
The following clarifications have been made to the phase 2 Schedule of Events: • Clarified that at concomitant medications are continuously monitored • Visit windows have been added • Removed incorrect vital sign assessments marked in dosing column • Clarified footnote describing phone visit requirements • Day 2 column shading was removed, as day 2 does not include a phone visit	To improve clarity of study schedule	Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #3 Table 4 Schedule of Events: Phase 2

Amendment 3

Description of Change	Brief Rationale	Section(s)
Primary virologic efficacy in phase 2 will be assessed using nasopharyngeal (NP) swab samples. NP swab sample collection has been correspondingly added. Provisional phase 3 secondary endpoints have also been updated for potential inclusion of NP swab samples.	To ensure adequate assessment of virologic efficacy.	Section 2.2 Secondary Objectives Section 4.1 Primary Endpoint Section 4.1 Secondary Endpoints Table 4 Schedule of Events: Phase 2 Section 6.1.2 Phase 2 Section 6.1.3 Phase 3 Figure 3 Study Flow Diagram, Phase 2 Section 9.2.3.1 Saliva, Nasal Swab, and Nasopharyngeal Swab Collection Section 11.4.3.2 Secondary Efficacy Analysis
Additional patients may be enrolled in phase 1 to replace patients who have missing or negative baseline virologic sample(s) or are missing ≥1 follow-up virologic sample(s).	To ensure adequate assessment of virologic efficacy.	Section 7.1 Number of Patients Planned Section 7.4 Replacement of Patients

Amendment 2

Description of Change	Brief Rationale	Section(s)
Grade 3 or 4 treatment-emergent AEs will be collected (phase 1 only)	Per health authority request	Section 3.2.1.3 Rationale for Primary Objectives Section 5.3 Safety Variables Section 6.1.1 Phase 1 Table 3 Schedule of Events: Phase 1 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #7 Section 9.1.3 Unscheduled Visits Section 9.2.4.2 Adverse Event Monitoring Section 10 Safety Evaluation and Reporting (and sub-sections therein) Section 11.4.5.1 Adverse events
Clarified objective, endpoint, and procedure for assessing viral resistance	Per health authority request	Section 2.3 Exploratory Objectives Section 4.3 Exploratory Endpoints Section 9.2.10.3 Virology
Clarified EC and IC terminology related to dose rationale	To clarify in vitro data descriptions	Section 3.2.2 Rationale for Dose Selection
Included secondary objective and endpoint to assess correlations in viral shedding across sample types	To understand differences in assessing virologic efficacy using distinct sampling sources	Section 2.2 Secondary Objectives Section 4.1 Secondary Endpoints Section 11.4.3.1 Primary Efficacy Analysis
Nasopharyngeal swab sampling added to day 11, 15, 18, and 25 (phase 1 only)	To provide matching sample types across time points	Section 6.1.1 Phase 1 Table 3 Schedule of Events: Phase 1 Figure 2 Study Flow Diagram, Phase 1 Figure 3 Study Flow Diagram, Phase 2
Study will be conducted in the US and other countries	To broaden reach of study	Section 6.1 Study Description and Duration

Description of Change	Brief Rationale	Section(s)
Added country as a stratification factor for randomization in phase 2	To ensure balance in study populations	Section 8.6. Method of Treatment Assignment Section 11.4 Statistical Methods
Screening for SARS-CoV-2 infection can be performed by any validated molecular diagnostic assay; historical record ≤72 hours of randomization is acceptable	To clarify acceptable screening criteria	Section 7.2.1 Inclusion Criteria, #2 Table 3 Schedule of Events: Phase 1 Table 4 Schedule of Events: Phase 2 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #5 Section 9.2.1.2 Molecular Diagnostic Test for SARS-CoV-2
For assessment of COVID-19 symptom onset during screening, symptoms are defined per investigator discretion	To clarify inclusion criterion	Section 7.2.1 Inclusion Criteria, #4
Endpoints in phase 1 related to intensive care unit (ICU) and mechanical ventilation moved to exploratory; other statistical clarifications made to primary and secondary efficacy analysis, multiplicity control, and interim analysis	To ensure consistency with planned statistical analysis	Section 4.1 Secondary Endpoints Section 4.3 Exploratory Endpoints Section 11.1 Statistical Hypothesis Section 11.2 Justification of Sample Size Section 11.4.3.2 Secondary Efficacy Analysis Section 11.4.4 Control of Multiplicity Section 11.5 Interim Analysis
Updated study stopping criteria	To provide additional details for study stopping and/or adaptations	Section 6.1.4.2 Study Stopping Criteria
The Independent Data Monitoring Committee (IDMC) will review both safety and efficacy data during the study	To clarify the planned IDMC review process	Section 6.2.1 Independent Data Monitoring Committee
Any unused or leftover biological samples collected during the study may be used for exploratory research; maximum time period of allowable storage ([redacted]) may be shorter per regional laws and regulations	To clarify the intended use and storage of samples	Section 9.2.8 Drug Concentration Measurements and Samples Section 9.2.9 Immunogenicity Measurements and Samples Section 9.2.10 Exploratory Pharmacodynamic/Biomarker Analyses [redacted]
The following operational changes and clarifications have been made: • Phone visits have a window of ±1 day • Day 29 visit may occur at any in-person location • Clarified that home-based visits may be done by home health staff	To provide additional flexibility for sample collection and assessments	Section 6.1.1 Phase 1 Section 6.1.2 Phase 2 Table 3 Schedule of Events: Phase 1 Table 4 Schedule of Events: Phase 2 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #3
Early termination visit will consist of day 29 assessments, with follow-up phone contact on day 29	To clarify early termination assessments	Section 1 Early Termination from the Study
Updated the list of targeted concomitant medications to be recorded	To ensure consistency with eCRF	Section 9.2.4.3 Record Targeted Concomitant Medications

Description of Change	Brief Rationale	Section(s)
Respiratory rate will only be measured in phase 1; temperature will not be measured rectally	To clarify required assessments	Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #6 Section 9.2.4.1 Vital Signs
Updated description of SE-C19 survey	To clarify the scoring system used	Section 9.2.10.8 Exploratory Patient-Reported Symptoms
Removed delineation of visit locations in Schedule of Events; visits may occur at any in-person location except where additional phone visits are indicated	To improve clarity of study schedule and design	Table 3 Schedule of Events: Phase 1 Table 4 Schedule of Events: Phase 2 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #3
Clarifications of study procedures	To improve clarity of procedures and planned analyses	Section 9.2.1.4 Medical History Section 9.2.7 Laboratory Testing Section 9.2.10.2 Serum and Plasma Biomarkers Section 9.2.10.4 Serological Immunoassays for Anti-SARS-CoV-2 Antibodies Section 9.2.10.5 Serum and Plasma for Research Section 9.2.10.4 Complement Section 9.2.10.7 Cytokines
Minor typographical, grammatical, editorial, and formatting updates	To ensure clarity, accuracy, and consistency	Throughout the document

Amendment 1

Description of Change	Brief Rationale	Section(s)
Mandatory sequestering is only applicable to patients in the phase 1 sentinel safety group	Clarification of study design	Section 6.1 Study Description and Duration Figure 2 Study Flow Diagram, Phase 1 Table 3 Schedule of Events: Phase 1 Table 4 Schedule of Events: Phase 2 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #2, #3 Section 9.2.3.2 COVID-19-related Medically-Attended Visit Details
Day 1 vital sign requirements (including pulse oximetry) added for patients in the phase 1 sentinel safety group	Per health authority request	Table 3 Schedule of Events: Phase 1 Table 4 Schedule of Events: Phase 2 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #8
Additional vital sign procedural details provided	To ensure study consistency with health authority request	Section 9.2.4.1 Vital Signs
Independent Data Monitoring Committee (IDMC) description updated	Operational details to be provided in the IDMC charter	Section 6.2.1 Independent Data Monitoring Committee
Editorial updates implemented	To ensure clarity, accuracy, and consistency	Section 8.7 Blinding

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACE2	Angiotensin-converting enzyme 2
ADA	Anti-drug antibody
ADE	Antibody-dependent enhancement
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CK-MB	Creatine kinase-MB
C_{max}	Maximum concentration
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
EC_{50}	Effective concentration of 50% viral neutralization
EC_{99}	Effective concentration of 99% viral neutralization
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
EUA	Emergency Use Authorization
FAS	Full analysis set
FDA	Food and Drug Administration
FIH	First-in-human
FcγR	Fc gamma receptor
GCP	Good clinical practice
GLP	Good laboratory practice
IRB	Institutional Review Board
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IDMC	Independent data monitoring committee
INR	International normalized ratio
IRT	Interactive response technology

IRWS	Interactive web response system
IV	Intravenous
IVIG	Intravenous immunoglobulin
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MAV	Medically-attended visit
MERS-CoV	Middle East respiratory syndrome coronavirus
mFAS	Modified full analysis set
NAb	Neutralizing antibodies
NCI	National Cancer Institute
NLR	Neutrophil-lymphocyte ratio
NT-proBNP	N-terminal pro B-type natriuretic peptide
PK	Pharmacokinetic
PT	Prothrombin time
RBD	Receptor binding domain
Regeneron	Regeneron Pharmaceuticals, Inc.
REGN10933+REGN10987	Co-administered REGN10933+REGN10987 combination therapy
RT-qPCR	Quantitative reverse transcription polymerase chain reaction
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TWA	Time-weighted average
WHO	World Health Organization
WOCBP	Women of childbearing potential

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Master Protocol Assessing the Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Patients with COVID-19
Site Locations	The study will be conducted in approximately 120 sites in the United States and other countries.
Principal Investigator	To be determined

Note: The phase 1 and phase 2 portions of the study have been completed. Therefore, this synopsis provides information pertaining to phase 3 only. Refer to the main text for information regarding phase 1 and phase 2.

Objectives

Primary

Cohort 1 (≥18 Years Old, Not Pregnant at Randomization)

- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo as measured by COVID-19-related hospitalizations or all-cause death.

Cohort 2 (<18 Years Old, Not Pregnant at Randomization)

- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- To further characterize the concentrations of REGN10933 and REGN10987 over time

Cohort 3 (Pregnant at Randomization)

- To evaluate the safety and tolerability of REGN10933+REGN10987

Secondary

Cohort 1

- To evaluate the impact of REGN10933+REGN10987 on the resolution of self-reported COVID-19 symptoms compared to placebo
- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo using various measures of COVID-19-related medically-attended visits, including COVID-19-related hospitalizations, emergency room visits, or all-cause death
- To describe the virologic effects of REGN10933+REGN10987 compared to placebo
- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- To further characterize the concentrations of REGN10933 and REGN10987 in serum over time
- To assess the immunogenicity of REGN10933 and REGN10987

Cohort 2

- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo using various measures of COVID-19-related medically-attended visits, including COVID-19-related hospitalizations or all-cause death
- To describe the virologic effects of REGN10933+REGN10987 compared to placebo
- To assess the immunogenicity of REGN10933 and REGN10987

Cohort 3

- To characterize the concentrations of REGN10933 and REGN10987 in serum over time
- To assess the immunogenicity of REGN10933 and REGN10987

Study Design	This is an adaptive, phase 1/2/3, randomized, double-blinded, placebo-controlled master protocol to evaluate the efficacy, safety, and tolerability of REGN10933+REGN10987 combination therapy in ambulatory patients (ie, outpatients) with COVID-19. In phase 3, eligible patients in cohort 1 and cohort 2 will be randomized 1:1:1 to a single dose of placebo or one of two dose levels of REGN10933+REGN10987. In cohort 1, REGN10933+REGN10987 dose levels will consist of 1200 mg and 2400 mg. In cohort 2, body-weight

	equivalents of these two dose levels will be used. Patients in cohort 3 will be randomized 1:1 to one of two dose levels of REGN10933+REGN10987 (ie, no randomization to placebo), at 1200 mg and 2400 mg or body-weight equivalents as applicable. Note that as of 25 February 2021 (per IDMC recommendation), patients will no longer be randomized to placebo. On the day of dosing, patients will have NP swabs taken for SARS-CoV-2 RT-qPCR testing and blood drawn for safety, drug concentration, immunogenicity, and exploratory analyses. After infusion, patients will be monitored for at least 1 hour and released from the study site, if medically appropriate. Patients <12 years of age will be monitored for at least 2 hours after infusion, with more frequent vital sign assessments. Targeted safety information and COVID-19-related medically-attended visit details will be collected on an ongoing basis; minimally, patients (or their caregivers) will be queried during weekly phone visits through the first 29 days of the study. For patients <12 years of age, a phone call will be made within 6 to 8 hours after completing the infusion to collect targeted safety information; these patients (or their caregivers) should be instructed to contact the site within 24 hours post-infusion if they experience any side effects. Patients (or their caregivers) will also be asked to notify study personnel as soon as possible about any unplanned medically-attended visits that occur during the study. Patients enrolled in cohort 1 will have NP swabs and blood samples collected approximately every week through day 29 and will provide self-reported information about COVID-19 symptoms through electronic surveys (both daily and weekly). A subset of patients in cohort 1 will be enrolled in a PK sub-study. [redacted] Patients enrolled in cohort 2 will also have NP swabs and blood samples collected approximately every week through day 29, with an NP swab additionally collected on day 3. To reduce overall patient burden of blood sampling in this younger cohort, the frequency of blood sample collection and the total amount of blood collected per visit will vary according to body weight. In addition, patients in this cohort will be randomly assigned to one of four staggered PK-ADA sampling schedules. This will be done according to a central randomization scheme using an interactive web response system (IWRS). Patients enrolled in cohort 3 will follow the schedule of events for either cohort 1 or cohort 2, depending on the age of the enrollee at randomization. However, additional drug concentration and immunogenicity samples will be collected for patients enrolled in cohort 3 who are ≥18 years old. After the final in-person visit, all cohorts will have 2 follow-up phone calls to collect safety information, including (when applicable) additional information regarding pregnancy outcome.
Study Duration	In phase 3, the duration of the study is 170 days for each patient.
End of Study Definition	The end of study is defined as the date when the last living patient completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).
Population	
Sample Size	Up to approximately 8500 patients will be required for phase 3 cohort 1. For cohort 2, up to approximately 180 patients will be required. No enrollment targets are planned for cohort 3.
Target Population	This study will enroll non-hospitalized patients who have a positive diagnostic test for SARS-CoV-2. In phase 3, patients must meet the following criteria to be eligible for inclusion in the study. Other inclusion criteria also apply and are described in the main text: • Meets 1 of the following 3 criteria: a. **Cohort 1:** ≥18 years of age and not pregnant at randomization b. **Cohort 2:** <18 years of age and not pregnant at randomization c. **Cohort 3:** Pregnant at randomization *Note: cohort 2 and cohort 3 will only be enrolled where permitted by local requirements*

- Has SARS-CoV-2-positive diagnostic test from a sample collected ≤72 hours prior to randomization, using a validated SARS-CoV-2 antigen, RT-PCR, or other molecular diagnostic assay and an appropriate sample such as nasopharyngeal [NP], nasal, oropharyngeal [OP], or saliva

  Note: Historical record of positive result is acceptable, as long as the sample was collected ≤72 hours prior to randomization.
- Has symptoms consistent with COVID-19, as determined by the investigator, with onset ≤7 days before randomization
- **Cohort 1 and Cohort 2 only:** has ≥1 risk factor for severe COVID-19

  Risk factors are defined as follows:

  a. Age ≥50 years **(cohort 1 only)**
  b. Obesity, defined as:

     BMI ≥30 kg/m^2 **(cohort 1 only)**

     BMI (kg/m^2) ≥95th percentile for age and sex based on CDC growth charts **(cohort 2 ≥2 years only)**
  c. Cardiovascular disease, including hypertension
  d. Chronic lung disease, including asthma
  e. Type 1 or type 2 diabetes mellitus
  f. Chronic kidney disease, including those on dialysis
  g. Chronic liver disease
  h. [Risk factor removed]
  i. Immunosuppressed, based on investigator's assessment

     Examples include cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anemia, thalassemia, and prolonged use of immune-weakening medications
  j. Any underlying genetic condition, neurologic condition, metabolic condition, or congenital heart disease deemed by the investigator to be a risk factor for severe COVID-19 **(cohort 2 only)**

A patient who meets any of the following criteria will be excluded from the study. Other exclusion criteria also apply and are described in the main text:

- Was admitted to a hospital for COVID-19 prior to randomization, or is hospitalized (inpatient) for any reason at randomization
- Has participated, or is participating, in a clinical research study evaluating COVID-19 convalescent plasma, mAbs against SARS-CoV-2 (eg, bamlanivimab), or intravenous immunoglobulin (IVIG) within 3 months or within 5 half-lives of the investigational product (whichever is longer) prior to the screening visit
- Prior, current, or planned future use of any of the following treatments: COVID-19 convalescent plasma, mAbs against SARS-CoV-2 (eg, bamlanivimab), IVIG (any indication), systemic corticosteroids (any indication), or COVID-19 treatments (authorized, approved, or investigational)

  Note: Prior use is defined as the past 30 days or within 5 half-lives of the investigational product (whichever is longer) from screening
- Prior use (prior to randomization), current use (at randomization), or planned use (within 90 days of study drug administration or per current CDC recommendations, as applicable) of any authorized or approved vaccine for COVID-19
- Has participated, is participating, or plans to participate in a clinical research study evaluating any authorized, approved, or investigational vaccine for COVID-19
- Has a known positive SARS-CoV-2 serologic test
- Has a positive SARS-CoV-2 antigen or molecular diagnostic test from a sample collected >72 hours prior to randomization

Treatments: Study Drug

Cohort 1 (and Cohort 3 Patients ≥18 Years)

- Co-administered REGN10933+REGN10987 combination therapy, 1200 mg (600 mg each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 2400 mg (1200 mg each of REGN10933 and REGN10987) IV single dose

Cohort 2 (and Cohort 3 Patients <18 Years)

REGN10933+REGN10987 1200 mg and 2400 mg treatment arms will be adjusted according to body weight, as defined as below. All doses, consisting of 1:1 REGN10933 and REGN10987, will be given as IV single dose (1200 mg dose equivalent; 2400 mg dose equivalent):

- ≥40 kg: 1200 mg; 2400 mg
- ≥20 kg to <40 kg: 450 mg; 900 mg
- ≥10 kg to <20 kg: 224 mg; 450 mg
- ≥5 kg to <10 kg: 120 mg; 240 mg
- ≥2.5 kg to <5 kg: 60 mg; 120 mg
- <2.5 kg: 30 mg; 60 mg

Endpoints

Primary

Cohort 1

- Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29

Cohort 2

- Proportion of patients with treatment-emergent serious adverse events through day 29
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29
- Concentrations of REGN10933 and REGN10987 in serum over time

Cohort 3

- Proportion of patients with treatment-emergent serious adverse events through day 29
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29

Secondary

Cohort 1

Key secondary endpoints *(other secondary endpoints are provided in the main text)*

- Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 through day 29
- Time to COVID-19 symptoms resolution

Cohort 2 and Cohort 3

There are no key secondary endpoints in cohort 2 and cohort 3. All secondary endpoints are descriptive; refer to the main text.

Procedures and Assessments

Procedures and assessments will include the following:

Efficacy

- COVID-19-related medically-attended visit details
- NP swabs for SARS-CoV-2 RT-qPCR

	Safety • Treatment-emergent SAEs, treatment-emergent AESIs (grade ≥2 IRRs, grade ≥2 hypersensitivity reactions, and any TEAE that led to a medically-attended visit), and treatment-emergent grade ≥3 AEs (in cohort 2 only) • Blood collection for safety labs • Vital signs and concomitant medications • Vital status • Pregnancy status, pregnancy outcome (women of childbearing potential only).
Statistical Plan	This section summarizes the statistical plan for primary and key secondary analyses of phase 3 cohort 1. For analysis of cohort 2 and cohort 3, refer to the main text. Note that cohort 2 and cohort 3 may continue to enroll after enrollment of cohort 1 has been completed.
Statistical Hypothesis	The statistical hypotheses for the primary endpoint of phase 3 cohort 1 are as follows: • H_0: The risk of a patient having ≥1 COVID-19-related hospitalization or all-cause death through day 29 for REGN10933+REGN10987 2400 mg group is the same as that for placebo • H_1: The risk of a patient having ≥1 COVID-19-related hospitalization or all-cause death through day 29 for REGN10933+REGN10987 2400 mg group is not the same as that for placebo
Justification of Sample Size	The sample size of phase 3 cohort 1 is based on having sufficient power to analyze the primary endpoint in the modified full analysis set (mFAS). Based on data from the phase 2 analysis involving the first 799 symptomatic patients enrolled, as well as blinded phase 3 data, the Sponsor assumes that 83% of randomized patients will have a positive SARS-CoV-2 RT-qPCR test at baseline (and can therefore be included in the mFAS). The Sponsor also assumes an event rate of 3.4% for COVID-19-related hospitalization or all-cause death among patients on placebo in the mFAS. The final primary efficacy analysis for the 2400 mg dose group versus placebo comparison will be performed based on patients randomized on or before 17 January 2021, which includes approximately 1503 randomized patients with COVID-19 risk factors per group in the 2400 mg dose group and the placebo group (1248 per group in the mFAS). With this sample size, the study will have approximately 76% power to detect a significant treatment effect in the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death in mFAS at a 2-sided α of 0.05, assuming 3.4% of patients in the placebo group and 1.7% of patients in the 2400 mg group have an event (ie, a 50% reduction with REGN10933+REGN10987 treatment). If there is a greater treatment difference, such as a 60% reduction, the study will have at least 90% power to detect a significant treatment effect in the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death. The final efficacy analysis of the 1200 mg dose group versus placebo comparison will be performed in approximately 1352 patients with COVID-19 risk factors per dose group (approximately 1122 per dose group estimated in the mFAS), representing the cohort of patients enrolled starting in Protocol Amendment 6 (ie, when the 1200 mg dose was introduced) through February 24, 2021, the last date that enrollment into the placebo group was allowed. This analysis will only include patients who were concurrently randomized to either the 1200 mg dose group or the placebo group. The study will have approximately 72% power to detect a significant treatment effect in the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death in the mFAS at a 2-sided α of 0.05 assuming 3.4% of patients in the placebo group and 1.7% of patient in the 1200 mg group have an event (ie, a 50% reduction). If there is a greater treatment difference, such as a 60% reduction, the study will have approximately 88% power to detect a significant treatment effect in the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death. From 25 February 2021 onward, the Sponsor plans to randomize up to 1500 patients 1:1 to either the 1200 mg dose group or the 2400 mg dose group, in addition to the patients already enrolled under protocol amendment 6 and protocol amendment 7, to have adequate precision to estimate the difference in the proportion of patients with a COVID-19-related hospitalization or death between the 2 dose groups. For example, assuming an event rate of 1.7% in each group, with a total of approximately 2100 concurrently randomized patients per arm (1744 per arm in mFAS) in 1200 mg and 2400 mg dose groups, a 2-sided 95% confidence interval for the difference will extend approximately 1% from the

observed difference. Blinded sample size re-estimation may be performed based on the pooled observed event rates.

Statistical Analysis

Efficacy Analysis Sets (Cohort 1)

Only patients with COVID-19 symptoms will be included in phase 3. All symptomatic patients from the 800th randomized symptomatic patient will be included in phase 3. For phase 3 cohort 1, the full analysis set (FAS) includes all randomized symptomatic patients and is based on the treatment allocated (as randomized). The FAS includes patients with and without risk factors for severe COVID-19.

In phase 3, the mFAS includes all randomized patients with a positive SARS-CoV-2 central lab-determined RT-qPCR test from nasopharyngeal (NP) swab samples at randomization, and with at least one risk factor for severe COVID-19 at baseline. If pre-dose virologic results from the qualitative test are missing, then results from post-dose sample may be used to determine the qualitative PCR status at baseline, as long as the sample was collected within 2 hours after starting the study drug infusion. The mFAS is based on the treatment allocated (as randomized). The seronegative mFAS is defined as all randomized patients with documented seronegative status at baseline in the mFAS.

For the analyses of the 1200 mg group comparing to placebo, only patients concurrently randomized (ie, after protocol amendment 6 is implemented) will be included in the above analysis sets.

Primary Efficacy Analysis (Cohort 1)

The primary efficacy endpoint for phase 3 cohort 1 is the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29, which will be compared between each dose group and placebo using the stratified Cochran-Mantel-Haenszel (CMH) test with country as a stratification factor. P-values from the stratified CMH test and 95% confidence intervals for the risk ratio and relative risk reduction (1-risk ratio) using Farrington-Manning method will be presented. Exact method for p-values and confidence intervals will be used if the expected frequencies in all cells are not at least 5. The primary analysis will be performed based on mFAS. As key secondary analyses, the same analyses will be performed for patients with high baseline viral load ($>10^6$ copies/mL) and for seronegative mFAS, and for proportion of patients with a COVID-19-related hospitalization or all-cause death from day 4 through day 29 in the mFAS. The comparison of 1200 mg dose group to placebo will include only the subset of placebo patients concurrently randomized with 1200 mg dose group. Sensitivity and supportive analyses will be described in the SAP.

Key Secondary Efficacy Analysis (Cohort 1)

Time to COVID-19 symptoms resolution will be analyzed using the stratified log-rank test with randomization strata as stratification factor. The analyses will be performed in the mFAS. Estimates of median times and associated 95% confidence intervals using the Kaplan-Meier method will be reported. The hazard ratio and 95% CI for time to COVID-19 symptoms resolution of COVID-19 symptoms endpoint will be estimated by the Cox regression model with terms for treatment group and randomization strata. The p-value from the stratified log-rank test will be reported. Patients who do not experience resolution of symptoms will be censored at the last observation time point. Patients who died or had COVID-19-related hospitalization prior to day 29 will be censored at day 29. Patients with a baseline raw score ≤3 will be censored at day 0. Patients with missing baseline assessment will not be included in the analysis. Subgroup analyses may be performed among patients with more than one risk factor, with high baseline viral load, or who are seronegative at baseline.

COVID-19 symptoms included in the analysis are as follows: Body aches such as muscle pain or joint pain, Chest pain, Chills, Cough, Diarrhea, Dizziness, Fatigue, Feverish, Headache, Loss of appetite, Loss of taste/smell, Nausea, pressure/tight chest, Red or watery eyes, Runny nose, Shortness of breath/difficulty breathing, Sore throat, Sputum/Phlegm, and Stomachache.

Time to COVID-19 symptoms resolution will be defined as time from randomization to the first day during which the subject scored 'no symptom' (score of 0) on all of the above symptoms except Cough, Fatigue, and Headache, which can be 'mild/moderate symptom' (score of 1) or 'no symptom' (score of 0).

1. INTRODUCTION

1.1. Emergence of SARS-CoV-2 and COVID-19

Coronaviruses are a family of enveloped, single-stranded RNA viruses. In recent decades, two highly pathogenic strains of coronavirus were identified in humans: severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). These viruses were found to cause severe, and sometimes fatal, respiratory illness (Cui, 2019) (Fehr, 2015).

In December 2019, pneumonia of unknown cause was identified in clusters of patients in Wuhan City, China. A novel enveloped RNA betacoronavirus – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – was identified in these patients, and the disease caused by SARS-CoV-2 infection was later designated coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO, 2020) (Zhu, 2020). Millions of SARS-CoV-2 infections have been confirmed worldwide, and the rapidly-spreading, worldwide outbreak has prompted the WHO to declare COVID-19 a pandemic and public health emergency of international concern.

1.2. Clinical Outcomes in Hospitalized Patients with COVID-19

Patients with COVID-19 are at risk for developing a variety of respiratory conditions, ranging from relatively mild symptoms to respiratory failure and death (Wu, 2020). Among hospitalized patients, intensive care and/or supplemental oxygen intervention (eg, mechanical ventilation) is often required, and reported fatality rates are high.

In a report from the Chinese Center for Disease Control and Prevention that included 44,500 confirmed infections, nearly 20% of patients presented with advanced respiratory symptoms (14% with dyspnea, hypoxia, and >50% lung involvement on imaging; 5% with respiratory failure, shock, or multiorgan failure) (Wu, 2020). Another analysis of patients with COVID-19 in China found that, among 1,099 hospitalized patients, 5% had been admitted to an intensive care unit (ICU), 2.3% required invasive mechanical ventilation, and 1.4% died. Among patients with advanced disease on admission (defined as pneumonia, hypoxemia, and tachypnea), these negative outcomes rose to 19%, 14.5%, and 8.1%, respectively (Guan, 2020). A report of 2634 hospitalized patients with COVID-19 in the United States identified similar clinical outcomes: 14.2% were admitted to an ICU, 12.2% required invasive mechanical ventilation, and 21% died (Guan, 2020). Other reports have found that approximately 20% to 30% of hospitalized patients with COVID-19 and pneumonia require intensive care for respiratory support (Richardson, 2020).

1.3. Ambulatory Care as a Potential COVID-19 Treatment Setting

Although severe COVID-19 can occur across all age groups, accumulating data have identified several factors that can place patients at risk of more serious illness and potentially lead to hospitalization, emergency room visits, or other medically-attended visits. These include age, pregnancy, as well as variety of comorbidities such as obesity and cardiovascular disease (Chen, 2020b). An anti-viral therapeutic that could be administered to ambulatory patients (ie, outpatients) has the potential to significantly reduce COVID-19-related medically-attended visits, particularly among those with 1 or more baseline risk factors Currently, there is a great need for therapies capable of reducing viral load and slowing or preventing COVID-19 disease progression.

1.4. The Role of Spike (S) Protein in SARS-CoV-2 Pathogenesis

Coronaviruses consist of an RNA genome packaged in nucleocapsid (N) protein surrounded by an outer envelope. The envelope is comprised of membrane (M) protein and envelope (E) protein, which are involved in virus assembly, and spike (S) protein, which mediates entry into host cells. S proteins form large trimeric projections, providing the hallmark crown-like appearance of coronaviruses. S protein trimers bind to a host receptor and, after priming by cellular proteases, mediate host–virus membrane fusion (Huang, 2020). The S protein appears to be central to viral infectivity by SARS-CoV-2. SARS-CoV-2 S protein binds the host receptor angiotensin-converting enzyme 2 (ACE2) with high affinity, and in cell assays and animal models can utilize ACE2 as a functional receptor for host cell entry (Hoffmann, 2020) (Ou, 2020) (Walls, 2020).

Blockade of host cell entry through the use of neutralizing antibodies against S protein is a viable mechanistic strategy shown to reduce viral infectivity of SARS-CoV and MERS-CoV (Jiang, 2020). In light of the likely pivotal role of S protein in the pathogenesis of SARS-CoV-2 (Datta, 2020), a number of efforts are underway to develop antibodies and vaccines that target the S protein of this novel coronavirus.

1.5. REGN10933+REGN10987: Human Monoclonal Antibodies that Target SARS-CoV-2 S Protein

Regeneron Pharmaceuticals, Inc (Regeneron) is currently developing human, neutralizing monoclonal antibodies (mAb)s directed against the S protein of SARS-CoV-2, for the treatment and prevention of SARS-CoV-2 infection. REGN10933 and REGN10987 are human, IgG1 mAbs that bind the receptor binding domain (RBD) of the SARS-CoV-2 S protein and block interaction with ACE2. REGN10933 and REGN10987 exhibit potent neutralization and can bind simultaneously to the S protein RBD. When co-administered as combination therapy, REGN10933+REGN10987 treatment is anticipated to neutralize SARS-CoV-2 with a reduced likelihood of viral escape due to genetic mutations. Importantly, these mAbs retain neutralization potency against multiple SARS-CoV-2 variants identified through clinical isolates, including recently-emerging variants such as the D614G variant, B.1.1.7 variant (first identified in the UK), and B.1.351 variant (first identified in South Africa) (Baum, 2020) (Korber, 2020) (Wang, 2021). REGN10933+REGN10987 combination therapy thus represents a promising therapeutic strategy to reduce SARS-CoV-2 viral load and COVID-19 disease progression.

1.6. A Randomized, Placebo-Controlled Study of Anti-SARS-CoV-2 S Protein Monoclonal Antibodies in Ambulatory Patients with COVID-19

Several therapeutic and preventative agents are under investigation for the treatment or prevention of COVID-19. While a number of these agents have received approvals or conditional authorizations (FDA, 2021) (EMA, 2021), there remains a significant unmet medical need for COVID-19 treatments. Multiple COVID-19 therapies will be required, both to address the medical requirements of distinct patient populations and to bolster treatment supplies as caseloads continue to rise. The availability of multiple treatment options, and the continued collection of data on conditionally authorized treatments, are both critically important in the setting of a global pandemic.

This is an adaptive, phase 1/2/3, randomized, double-blinded, placebo-controlled master protocol to further evaluate the efficacy and safety of co-administered REGN10933+REGN10987 in ambulatory patients (ie, outpatients) with COVID-19.

For more information regarding the rationale for the study design and dose selection, refer to Section 3.2. Additional background information on the study drugs and the overall development program can be found in the Investigator's Brochure.

2. STUDY OBJECTIVES

2.1. Primary Objectives

Phase 1

The primary objectives of phase 1 are:

- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- To evaluate the virologic efficacy of REGN10933+REGN10987 compared to placebo in reducing viral load of SARS-CoV-2

Phase 2

The primary objective of phase 2 is to evaluate the virologic efficacy of REGN10933+REGN10987 compared to placebo in reducing viral load of SARS-CoV-2.

Phase 3

Cohort 1 (≥18 Years Old, Not Pregnant at Randomization)*

The primary objective is to evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo as measured by COVID-19-related hospitalizations or all-cause death.

Cohort 2 (<18 Years Old, Not Pregnant at Randomization)*

The primary objectives are:

- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- To further characterize the concentrations of REGN10933 and REGN10987 in serum over time

Cohort 3 (Pregnant at Randomization)*

The primary objective is to evaluate the safety and tolerability of REGN10933+REGN10987.

*Refer to Section 7.2.1 for study cohort definitions.

2.2. Secondary Objectives

Phase 1

The secondary objectives of phase 1 are:

- To evaluate additional indicators of virologic efficacy of REGN10933+REGN10987 compared to placebo
- To estimate the clinical efficacy of REGN10933+REGN10987 compared to placebo
- To compare quantitative reverse transcription polymerase chain reaction (RT-qPCR) results acquired with different sample types (nasopharyngeal [NP], nasal, and saliva)
- To characterize the PK profiles of REGN10933 and REGN10987 in serum
- To assess the immunogenicity of REGN10933 and REGN10987

Phase 2

The secondary objectives of phase 2 are:

- To evaluate additional indicators of virologic efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo
- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- To characterize the concentrations of REGN10933 and REGN10987 in serum over time
- To assess the immunogenicity of REGN10933 and REGN10987

Phase 3

The secondary objectives of phase 3 are:

Cohort 1*

- To evaluate the impact of REGN10933+REGN10987 on the resolution of self-reported COVID-19 symptoms compared to placebo
- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo using various measures of COVID-19-related medically-attended visits, including COVID-19-related hospitalizations, emergency room visits, or all-cause death
- To describe the virologic effects of REGN10933+REGN10987 compared to placebo
- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- To further characterize the concentrations of REGN10933 and REGN10987 in serum over time
- To assess the immunogenicity of REGN10933 and REGN10987

Cohort 2*

- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo using various measures of COVID-19-related medically-attended visits, including COVID-19-related hospitalizations or all-cause death
- To describe the virologic effects of REGN10933+REGN10987 compared to placebo
- To assess the immunogenicity of REGN10933 and REGN10987

Cohort 3*

- To characterize the concentrations of REGN10933 and REGN10987 in serum over time
- To assess the immunogenicity of REGN10933 and REGN10987

*Refer to Section 7.2.1 for study cohort definitions.

2.3. Exploratory Objectives

The exploratory objectives (phase 1, phase 2, and phase 3) are:

- To evaluate viral variants at baseline and post-treatment
- To explore the potential association of baseline humoral immune response to SARS-CoV-2 on response to REGN10933+REGN10987
- To evaluate the effects of REGN10933+REGN10987 compared to placebo on generation of a humoral immune response to SARS-CoV-2 (as measured by anti-SARS-CoV-2 N protein)
- To explore the effects of REGN10933+REGN10987 on measures of SARS-CoV-2 infectivity as assessed in experimental laboratory assays
- To explore biomarkers predictive of REGN10933+REGN10987 safety, efficacy, and/or disease progression and COVID-19 clinical outcomes
- To explore the underlying mechanisms of action and biology of REGN10933+REGN10987, SARS-CoV-2, and COVID-19
- To explore relationships between REGN10933+REGN10987 exposure and selected efficacy endpoints, safety endpoints, and/or biomarkers
- To evaluate the impact on self-reported symptoms of REGN10933+REGN10987 compared to placebo

Additional exploratory objective for phase 1 only:

- To evaluate additional indicators of clinical efficacy of REGN10933+REGN10987 compared to placebo

Additional exploratory objective for phase 3 only:

- To assess the clinical efficacy of different dose levels of REGN10933+REGN10987, as measured by COVID-19-related hospitalizations or all-cause death

- To describe the relationship between virologic effects of REGN10933+REGN10987 and risk of COVID-19-related medically-attended visit or all-cause death
- [redacted]
- To evaluate the impact of REGN10933+REGN10987 on the resolution of self-reported COVID-19 symptoms compared to placebo (cohort 2 age ≥12 years)
- To describe the clinical outcomes of patients treated with REGN10933+REGN10987 using various measures of COVID-19-related medically-attended visits, including COVID-19-related hospitalizations or all-cause death (cohort 3)

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

Phase 1

Treatment of ambulatory patients with COVID-19 with REGN10933+REGN10987 will be tolerated and will reduce viral load.

Phase 2

Treatment of ambulatory patients with SARS-CoV-2 infection with REGN10933+REGN10987 will reduce viral load.

Phase 3

Treatment of ambulatory patients (≥18 years) with COVID-19 with REGN10933+REGN10987 will improve clinical outcomes.

Treatment of ambulatory patients (<18 years) with COVID-19 with REGN10933+REGN10987 will be well tolerated.

Information concerning statistical hypotheses can be found in Section 11.1.

3.2. Rationale

3.2.1. Rationale for Study Design

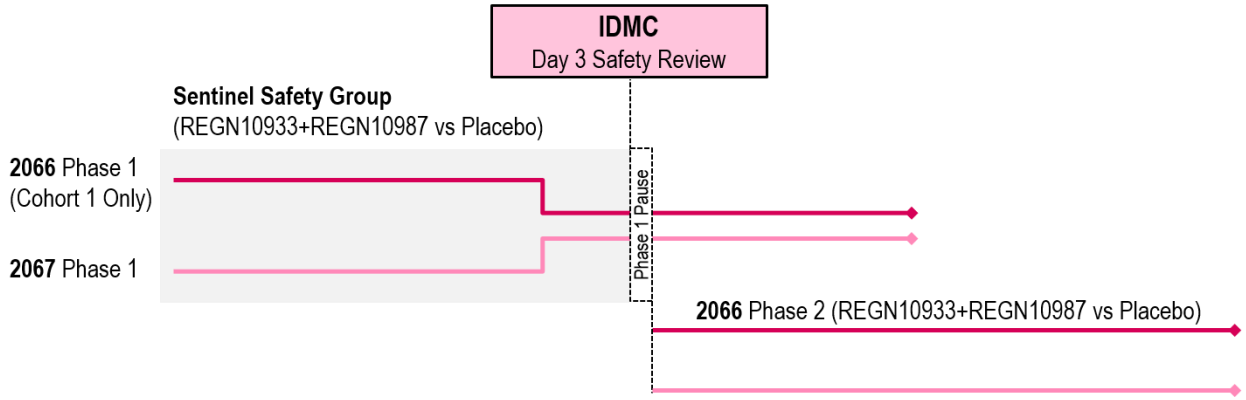
This randomized, double-blinded, placebo-controlled, adaptive phase 1/2/3 master protocol will assess the safety, tolerability, and efficacy of REGN10933+REGN10987 in ambulatory patients with COVID-19 (including, in phase 2, those with asymptomatic SARS-CoV-2 infection). The multicenter conduct of this study will enable generalizable evidence of the safety, tolerability, and efficacy of these investigational mAbs for COVID-19.

3.2.1.1. Phase 1 Sentinel Safety Group

This master protocol will include a first-in-human (FIH) phase 1 study to evaluate safety and tolerability. Driven by the medical urgency of the COVID-19 pandemic, the process described below is designed to maximize efficient enrollment of eligible patients while optimizing safety of FIH exposure with limited preclinical data.

Phase 1 will include a sentinel safety group (Figure 1), where the initial safety data up to day 3 will be reviewed by an independent data monitoring committee (IDMC).

Figure 1: Phase 1 Sentinel Safety Group



Patients in this sentinel safety group can be derived from either of 2 concurrent FIH studies, where the safety and tolerability of REGN10933+REGN10987 will be evaluated:

- R10933-10987-COV-2066, in hospitalized adult patients with COVID-19
- R10933-10987-COV-2067, in ambulatory adult patients with COVID-19

For IDMC review, patients will be pooled together from the phase 1 portions of either of the 2 studies. Once safety data have been collected on day 3 for approximately 30 patients (from one or both of the studies combined), the IDMC will review the data.

Note that phase 1 enrollment will pause during the IDMC review.

Initiation of phase 2 enrollment is contingent upon IDMC review of phase 1 data from the sentinel safety group. Study stopping criteria are outlined in Section 6.1.4.2.

After the IDMC reviews and provides a positive recommendation for the phase 1 sentinel safety group, enrollment of studies assessing REGN10933+REGN10987 (including REGN10933+REGN10987 treatment arms in phase 2 of this study and R10933-10987-COV-2066) may begin.

Once phase 2 of this study is active, phase 1 will continue to enroll to completion. However, phase 2 enrollment does not require the completion of phase 1 enrollment.

Review of Sentinel Safety Group (information added to protocol in amendment 5)

A blinded Sponsor analysis of the sentinel safety group data showed that REGN10933+REGN10987 was well tolerated in hospitalized or ambulatory adult (≥18 years) patients with COVID-19, with no hypersensitivity reactions or infusion-related reactions reported. Vital signs and laboratory assessments did not identify any safety signals. IDMC review

recommended to continue enrollment in the studies after unblinded data review. For more details, refer to the Investigator's Brochure.

3.2.1.2. Adaptive Master Protocol Design

The study utilizes an adaptive master protocol design. The adaptive design has been selected to maximize the efficiency of identifying early signs of efficacy, increase the efficiency of studying multiple therapeutic combinations, and avoid the use of ineffective dose levels in patients with COVID-19.

Due to the novel nature of the COVID-19 pandemic, efficacy endpoints are not well established, and the standard-of-care is expected to evolve over time. The adaptive design of this study allows for the assessment of virologic and clinical efficacy endpoints in phase 2, which are then seamlessly confirmed in the phase 3 portion of the study, as well as evaluating the benefit and risk of the different treatment arms.

This master protocol will allow for treatment arm(s) to be dropped if there is a clinically meaningful imbalance between treatment arms in the incidence of SAEs or the incidence of AESIs, or if there is a meaningful imbalance between treatment arms regarding efficacy endpoints.

The design will allow for the addition of new treatment arms at different dose levels of REGN10933+REGN10987, the addition of treatment arms with other anti-SARS-CoV-2 S protein mAbs as they become available for clinical testing (umbrella design), refinement of disease characteristics of eligible study populations (basket design), as well as other adaptations, including determination of phase 3 primary endpoints and phase 3 sample size estimation.

3.2.1.3. Rationale for Phase 1 and Phase 2 Objectives

Safety and Tolerability

The primary objective of phase 1 is safety and tolerability, evaluated by targeted collection of treatment-emergent serious adverse events (SAEs) throughout the study and treatment-emergent adverse events of special interest (AESIs) through day 29. In addition, grade 3 and grade 4 treatment-emergent adverse events (TEAEs) will be recorded in phase 1 to inform safety assessments in later phases.

Many patients who are ambulatory and experiencing relatively early stages of COVID-19 may nevertheless present with complicated disease presentation at baseline or could quickly and unexpectedly deteriorate and progress to have a complicated disease presentation. As such, their TEAE profile could be complex and dynamic. Accurately collecting such a large volume of TEAEs could impose unnecessary burden on an already over-strained healthcare system, and frequent exposure to infected patients could increase the risk of infection to the study staff.

Evaluating treatment-emergent SAEs and treatment-emergent AESIs (grade ≥2 hypersensitivity reactions and grade ≥2 infusion-related reactions), as well as targeted treatment-emergent grade 3 or 4 TEAEs in phase 1, will provide the most relevant safety information to adequately evaluate the safety and tolerability of REGN10933+REGN10987. This subset of treatment-emergent grade 3 or 4 TEAEs, treatment-emergent SAEs and treatment-emergent AESIs encompasses the key safety concern that would be expected for mAbs against exogenous targets and help evaluate unexpected SAEs. Regeneron plans to collect data on non-serious TEAEs (as well as serious TEAEs) in a parallel-conducted prophylaxis study (R10933-10987-COV-2069) and a repeated

dose study in adult volunteers (R10933-10987-HV-2093) with REGN10933+REGN10987, where the study population will not have a complicated disease presentation and there is a significantly lower risk of overburdening the healthcare delivery system.

Virologic Efficacy

The primary mechanism of action of REGN10933+REGN10987 is blockade of the S protein RBD interaction with ACE2, leading to decreased infection of host cells. Blocking viral entry would result in reductions in SARS-CoV-2 RNA replication and corresponding viral load in affected tissues. In phase 1 and phase 2, the primary virologic endpoint will therefore evaluate, as proof of mechanism, the ability of REGN10933+REGN10987 to reduce viral load in the upper respiratory tract. Day 22 (21 days after dosing) was chosen as the cutoff date for this analysis, based on accumulating evidence that this time period approaches the lower limit of detection in samples collected from the upper respiratory tract in patients spontaneously recovering from COVID-19 (He, 2020). In phase 2, virologic efficacy will also be evaluated in asymptomatic patients with laboratory-confirmed SARS-CoV-2 infection. The 21-day assessment period is similarly appropriate for this cohort, based on evidence that peak viral load occurs just before or soon after the onset of COVID-19 symptoms (Cao, 2020) (Wang, 2020c).

Prior to unblinding for analysis of interim phase 1/2 data and analysis of phase 2 data, the cutoff date of the primary virologic endpoint was pre-specified in the statistical analysis plan (SAP) as day 7 rather than day 22. This was done as the result of the phase 1/2 analysis, which showed that the majority of viral clearance had occurred prior to day 7. For more information, refer to Section 3.2.1.5 and (Weinreich, 2020).

Clinical Efficacy

Clinical efficacy will also be evaluated. Patients enrolled in this study will be in the early phase of their infection (Section 7.2.1), and are therefore expected to be presymptomatic or have milder, less advanced disease compared with individuals diagnosed at later stages of COVID-19. By directly targeting host entry by SARS-CoV-2, REGN10933+REGN10987 may impact the early stages of the disease course, preventing symptom onset, mitigating early disease progression, and reducing the likelihood that patients will experience the more advanced symptoms associated with hospitalization and/or other urgent medical visits. Phase 2 will therefore assess the proportion of patients requiring COVID-19-related medically-attended visits (defined in Section 9.2.3.2) subsequent to their initial disease diagnosis and released home.

3.2.1.4. Stratification According to Risk of Hospitalization (Phase 2)

In phase 2, randomization will be stratified based on risk factors for hospitalization due to COVID-19 (refer to Section 8.6 for complete definition of phase 2 risks factors; also note that other stratification factors will be used as described in Section 8.6).

Although more advanced COVID-19 illness can occur in individuals of all ages, it primarily occurs in older adults or those with underlying medical conditions, including cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease, obesity (body mass index [BMI] $\geq$30 kg/m^2), cancer, and chronic kidney disease (CDC, 2020b) (Lighter, 2020) (Wu, 2020) (Zhou, 2020).

Hospitalization rates for COVID-19 increase with age, with one study reporting a 1% hospitalization rate for those 20 to 29 years, 4% rate for those 50 to 59 years, and 18% for those >80 years of age (Liu, 2020). Moreover, the majority of those hospitalized or in ICUs are older

adults. Among 4,226 COVID-19 cases reported in the United States during February and March 2020, for example, 45% of hospitalizations and 53% of ICU admissions for COVID-19 were among adults ≥65 years of age (CDC, 2020c).

In addition to older patients, younger patients with underlying medical conditions may be at higher risk for hospitalization due to COVID-19. Among 7,162 patients reported in the United States with COVID-19 who had data available on their underlying health conditions, for example, patients with underlying conditions were hospitalized at higher rates compared to those without underlying conditions (27.3% to 29.8% compared to 7.2% to 7.8%). The most common underlying conditions in the study were diabetes mellitus, cardiovascular disease and chronic lung disease (CDC, 2020b).

Obesity is prevalent condition that may also be a risk factor for hospitalization with COVID-19, with one study reporting that young obese patients (BMI ≥30 kg/m^2) were more likely to be hospitalized or admitted to an ICU compared to young patients who were not obese (Lighter, 2020). In the United States, nearly 40% of adults are obese and may be at higher risk of hospitalization due to COVID-19 (CDC, 2017).

3.2.1.5. Rationale for Phase 3 Adaptations

A summary of the most substantial phase 3 adaptations is provided in Table 1. These adaptations are being implemented based on available data from phase 1 and phase 2, which are summarized in the sub-sections below (and, for dose selection, in Section 3.2.2.2) and in the Investigator's Brochure. Modifications to these phase 3 adaptations were subsequently made in response to health authority feedback and are captured in the table below.

Table 1: Summary of Main Phase 3 Adaptations

Study Component	Adaptation[1]
Patient Eligibility	• Patients from 0 to <18 years will be enrolled as a separate cohort (cohort 2), where permitted by local requirements. Patients ≥18 years old will be enrolled in cohort 1 • Patients who are pregnant or breastfeeding can enroll in the study. Patients who are pregnant at randomization will be enrolled in cohort 3, where permitted by local requirements • Patients in cohort 1 and cohort 2 must have ≥1 risk factor for severe COVID-19 • Patients with a known positive SARS-CoV-2 serology test will be excluded • Patients with a positive SARS-CoV-2 antigen test or molecular diagnostic test from a sample collected >72 hours prior to randomization will be excluded • Patients with active infection with influenza or other non-SARS-CoV-2 respiratory pathogen, confirmed by a diagnostic test, will be excluded
Treatment Arms	• For cohort 1, the treatment arms will be REGN10933+REGN10987 2400 mg IV, REGN10933+REGN10987 1200 mg IV, and placebo. Note that as of 25 February 2021 (per IDMC recommendation), patients in this cohort will no longer be randomized to placebo.

	• For cohort 2, the treatment arms will be weight-tiered dosing that matches REGN10933+REGN10987 2400 mg IV, REGN10933+REGN10987 1200 mg IV, and placebo IV. Note that as of 25 Feb 2021, patients in this cohort will no longer be randomized to placebo. • For cohort 3, the treatment arms will be REGN10933+REGN10987 2400 mg IV and REGN10933+REGN10987 1200 mg IV. No placebo arm will be used. Weight-tiered dosing will be used for patients <18 years of age.
Objectives /Endpoints	• For cohort 1, primary endpoint will be the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death. The key pre-specified secondary endpoints include time to COVID-19 symptoms resolution. A hierarchical testing strategy will be used to control for multiplicity. • For cohort 2 and cohort 3, the primary endpoints will be safety/tolerability • For cohort 2, secondary endpoint analyses will be descriptive • Virologic analyses for all cohorts will be secondary and descriptive [redacted]
Sample Size	• Enrollment in phase 3 cohort 1 is anticipated to be up to approximately 8500 patients • Cohort 2 will enroll up to approximately 180 patients; there will be a minimum enrollment of 20 patients <10 kg (10 per treatment group) and 20 patients between ≥10 kg and <40 kg (10 per treatment group) • No minimum or maximum enrollment is planned for cohort 3 • Cohort 2 and cohort 3 may continue to enroll after enrollment of cohort 1 has been completed

[1] Phase 3 adaptations were initially implemented in protocol amendment 6. Modifications to the phase 3 adaptations were subsequently implemented in response to health authority feedback (protocol amendment 7) and prior to phase 3 statistical analyses (protocol amendment 8). Refer to the amendment history table for more detailed information.

Virologic Efficacy

An interim analysis of pooled phase 1/2 data (n=275) was conducted to assess preliminary virologic and clinical efficacy of REGN10933+REGN10987. Among patients who were SARS-CoV-2 seronegative at baseline, those who received REGN10933+REGN10987 had a greater reduction in viral load through day 7 compared with those who received placebo, as measured by time-weighted average (TWA) change from baseline. For example, seronegative patients receiving either REGN10933+REGN10987 2400 mg or 8000 mg (combined analysis) had a TWA viral load change of -1.94 $\log_{10}$ copies/ml, versus -1.37 $\log_{10}$ copies/ml in the placebo arm (difference between combined dose group and placebo, -0.56 $\log_{10}$ copies/mL; nominal p=0.0165). Post-hoc analysis of virologic outcomes by baseline viral load found that patients with the highest viral load at baseline had the largest treatment benefit.

A subsequent analysis of the remaining patients in phase 2 (n=524) formally corroborated the virologic efficacy findings observed in the phase 1/2 analysis in a prespecified and statistically rigorous manner. There was a statistically significant reduction in the TWA change from baseline in viral load (log_{10} copies/mL) from day 1 through day 7 in patients treated with either dose of REGN10933+REGN10987 or the combined dose group (-1.66 log_{10} copies/ml) compared to placebo (-1.30 log_{10} copies/ml) (difference between combined dose group and placebo, -0.36 log_{10} copies/mL; p=0.0003). Statistically significant reductions were observed in the overall population that were SARS-CoV-2 RT-qPCR positive at baseline. and were more pronounced in those with high baseline viral load (>10^7 copies/mL or >10^6 copies/mL) or those who were seronegative at baseline. Descriptively, the greater reduction in viral load with REGN10933+REGN10987 treatment compared to placebo could be observed as early as 2 days post-treatment (the first time point assessed) and was maintained at each subsequent time point through day 11, when the mean viral load in each of the REGN10933+REGN10987 treatment groups fell below the lower limit of quantification (<2.87 log_{10} copies/mL).

By contrast, patients who were seropositive at baseline had mean baseline viral loads approximately 3-log lower than patients who were seronegative at baseline, and the change from baseline in viral load through day 7 for seropositive patients treated with either dose of REGN10933+REGN10987 was similar to the reduction in patients treated with placebo. These results suggest that the true benefit of a potent antiviral might be concentrated in the higher risk groups (eg, seronegative at baseline and higher baseline viral load).

Clinical Efficacy

The above virologic data collectively provide definitive evidence that REGN10933+REGN10987 markedly enhances SARS-CoV-2 viral clearance. Moreover, data from a pooled phase 1/2 analysis indicate that the viral load reduction translated into clinical benefit by significantly reducing COVID-19-related MAVs, defined as hospitalizations, ER visits, urgent care visits, or physician office or telemedicine visits for COVID-19. Specifically, a prespecified and multiplicity-controlled analysis of pooled phase 1/2 data in symptomatic patients who were SARS-CoV-2 RT-qPCR positive at baseline (n=799; mFAS=665) showed a statistically significant reduction in MAVs in the REGN10933+REGN10987 treated groups compared to placebo (2.8% combined dose groups vs 6.5% placebo; p=0.0240). Most of the MAVs occurred in patients who were higher risk, defined as seronegative at baseline, had higher baseline viral load, or had at least 1 pre-existing risk factor for severe COVID-19 (eg, age >50 years old, obesity, co-morbid conditions). In exploratory analyses, treatment with REGN10933+REGN10987 showed the greatest benefit in these high-risk groups, with reductions in the proportion of patients with MAVs compared to placebo of 62% (3.2% combined treatment versus 8.5% placebo) for those with baseline viral loads >10^4 copies/mL, 65% (3.4% combined treatment versus 9.7% placebo) for those who were seronegative at baseline, and 72% (2.6% combined treatment versus 9.2% placebo) for those who had at least 1 risk factor for severe COVID-19. Treatment with REGN10933+REGN10987 did not reduce MAVs for those who were seropositive at baseline (2.9% combined treatment versus 1.9% placebo) or for those who were without pre-existing risk factors for severe disease (2% combined treatment versus 1.9% placebo), suggesting that MAVs in these groups are less modifiable with treatment.

Considering the clinical benefits observed in phase 2, phase 3 will focus on confirming the clinical benefit of REGN10933+REGN10987 in reducing the risk of having a COVID-19-related

hospitalization or all-cause death for high-risk patients, thereby demonstrating the clinical benefit of reducing viral burden. Virologic secondary analyses will be conducted during phase 3, but these will be descriptive in nature.

Requirement of ≥1 Risk Factor for Severe COVID-19

The placebo-treated patients in the phase 1/2 portion of the study provided key insights into the natural history of COVID-19. Patients who were seronegative at baseline or who had at least 1 risk factor for severe COVID-19 had higher baseline viral loads compared to those who were seropositive or those who did not have pre-existing risk factors for severe disease. These patients took longer to reduce viral load and accounted for the majority of patients with MAVs. As described above, it was also these high-risk patients that had the greatest benefit with REGN10933+REGN10987 treatment in reducing MAVs. Treatment with REGN10933+REGN10987 did not appear to reduce MAVs in patients who were seropositive at baseline or in patients without risk factors for severe disease, suggesting the true benefit of treatment is in patients who have not yet mounted a sufficient immune response or have baseline risk factors for severe disease. Based on these very important learnings from the available data and considering that risk factors can readily be assessed by the treating provider without additional testing, adult patients enrolled in phase 3 subsequent to amendment 6 will be required to have at least one risk factor for severe COVID-19.

Risk factors for COVID-19 that will be applied to the study populations in phase 3 are defined in Section 7.2.1. These risk factors encompass the CDC definition of "at increased risk" and "might be at an increased risk" patients for severe COVID-19. Modifications to this list of risk factors have been made for phase 3. Pregnant women are included because pregnancy is considered a risk factor based on accumulating evidence that women who are pregnant are at increased risk for severe COVID-19 (Ellington, 2020) (Knight, 2020). Additional examples of immunosuppressed patients have also been added to more fully capture those noted to be at risk according to the CDC's definition.

In addition to the above risk factors, other modifications to eligibility criteria have been made in phase 3 to ensure further that at-risk patients are included. Although serological testing for negative serostatus will not be required for study entry, patients who have a known history SARS-CoV-2 infection prior to this study (demonstrated by a positive SARS-CoV-2 serology, antigen, molecular diagnostic test or other diagnostic assay other than the one used for eligibility into this study) will be excluded. Similarly, patients who report or have a known history of COVID-19 any time prior to the current episode of COVID-19 will be excluded.

Inclusion of Patients Under 18 Years of Age

Patients age 0 to <18 years with symptomatic COVID-19 and at least 1 risk factor for severe COVID-19 (defined in Section 7.2.1) will be included in the phase 3 portion of the study as a separate cohort to assess the safety, PK, immunogenicity, and efficacy of REGN10933+REGN10987.

Most children with COVID-19 seem to experience mild disease that can be managed symptomatically in the outpatient setting. However, children with risk factors including underlying medical conditions such as obesity, diabetes, chronic lung disease, or immunosuppression might be at increased risk for severe COVID-19 (Kim, 2020) (Shekerdemian, 2020). Surveillance data reported to CDC through May 2020 indicated that the COVID-19-related hospitalization rate

among children 0 to 9 years and 10 to 19 years old with underlying health conditions was approximately 6 times greater compared to children in the same age group with no reported underlying conditions (0 to 9 years, 22.3% versus 3.7%; 10 to 19 years, 14.9% versus 2.3%, respectively), and was similar to the hospitalization rate reported in adults, especially younger adults (eg, 20 to 29 years old), with and without underlying health conditions (17.5% versus 2.7%) (Stokes, 2020). Additionally, according to COVID-NET, a population-based surveillance for laboratory-confirmed COVID-19–associated hospitalizations in 99 counties in 14 states in the US, pediatric patients <12 years accounted for 58.2% of all hospitalized children and adolescents age 12 to 17 years accounted for 42% of all hospitalized children reported to COVID-NET between 1 Mar 2020 to 25 Jul 2020 (Kim, 2020).

Based on the phase 2 data described above, high-risk pediatric patients with COVID-19 could benefit from the anti-viral activity of REGN10933+REGN10987 and the potential clinical benefit of reducing COVID-19-related MAVs.

Since the rates of MAVs in pediatric patients with COVID-19 are unknown, these patients will be enrolled as a separate cohort and will not contribute to the primary efficacy endpoint. Instead, the primary objective for cohort 2 will be safety, with MAVs as a descriptive secondary objective.

REGN10933+REGN10987 mAbs are directed against an exogenous antigen, administration of REGN10933+REGN10987 and thus is not anticipated to affect endogenous pathways. Therefore, the safety profile in children is expected to be similar to that observed in adults. Safety data is reviewed in a continuous manner by the sponsor (blinded data) and by the IDMC (unblinded data).

Inclusion of Pregnant Women

Pregnant women are reported to be at an increased risk for severe COVID-19. Surveillance data reported to the CDC from January to June 2020 reported that pregnant women with COVID-19 were more likely to be hospitalized compared to nonpregnant women (31.5% versus 5.8%, respectively) (Ellington, 2020). Data reported to CDC through September 2020 showed that compared with nonpregnant women, pregnant women were more frequently admitted to an ICU (10.5 versus 3.9 per 1,000 cases; adjusted risk ratio = 3.0; 95% CI = 2.6–3.4), received invasive ventilation (2.9 versus 1.1 per 1,000 cases; adjusted risk ratio = 2.9; 95% CI = 2.2–3.8) and received ECMO (0.7 versus 0.3 per 1,000 cases; adjusted risk ratio = 2.4; 95% CI = 1.5–4.0) (Zambrano, 2020). Partly based on these data, the CDC considers pregnancy among the risk factors that places patients "at increased risk" for severe COVID-19. These outcome data suggest pregnant women could benefit from the anti-viral activity of REGN10933+REGN10987 and potential clinical benefit of reducing COVID-19-related MAVs. As such, pregnant women will be included in the phase 3 portion of the trial. These patients will be included as a separate double-blinded cohort, randomized only to different dose levels of REGN10933+REGN10987 (see Section 8.6 for details). The absence of a placebo arm will help to ensure that adequate descriptive safety information is collected for study drug in a population whose enrollment is anticipated to be relatively small and thus preclude hypothesis-driven analysis.

As an added safety measure in phase 3, for newborn infants of patients who were treated in the study and were pregnant at randomization or became pregnant at any time in the study, the incidence and outcome of any SARS-CoV-2 infection in these infants will be collected during follow-up phone calls. This collection is in addition to standard collection of pregnancy outcome information (Section 10.1.3).

[redacted]

Phase 3 Sample Size Adjustment

In light of the modifications to the phase 3 primary endpoint, adjustments to the phase 3 sample size were necessary to ensure adequate power to evaluate the primary endpoint. Refer to Section 11.2 for more information on sample size justification.

3.2.2. Rationale for Dose Selection

3.2.2.1. Phase 1 and Phase 2 Dose Selection

Phase 1 and phase 2 will assess a single IV dose of REGN10933+REGN10987 as combination therapy administered in a 1:1 ratio. The 1:1 ratio for REGN10933+REGN10987 is thought to be appropriate as these are non-competing mAbs targeting non-overlapping epitopes of the RBD of the S protein of SARS-CoV-2, with similar in vitro binding and neutralization properties (for more information, refer to the Investigator's Brochure). These study phases will evaluate the co-administered REGN10933+REGN10987 as combination therapy at an initial dose level of 2400 mg (1200 mg per mAb), which is expected to be an efficacious dose (see below). The study phases will also evaluate REGN10933+REGN10987 at a higher dose, 8000 mg (4000 mg per mAb), in the event that a higher dose is required for efficacy.

Cellular entry of coronaviruses depends on binding of the S protein to a specific cellular receptor and subsequent S protein priming by cellular proteases. ACE2 is the receptor for cellular entry of SARS-CoV-2 and its gene expression has been reported in the lungs, particularly in type-2 alveolar epithelial cells and bronchial airway epithelium (Xu, 2020). The strategy taken for dose selection in this study was to identify a target concentration in lung epithelial lining fluid (ELF) that approximates the effective concentration of 99% viral neutralization (EC_{99})* observed against live virus SARS-CoV-2 and to then identify a dose that will meet or exceed this concentration in lung ELF. The EC_{99} against SARS-CoV-2 is 0.14 µg/mL (REGN10933), 0.78 µg/mL (REGN10987), and 0.01 µg/mL (REGN10989).

An average lung ELF-to-serum mean C_{max} ratio of ~0.15 has been reported for other exogenous IgG1 mAbs for the treatment of *Staphylococcus aureus* lung infections (Magyarics, 2019). It is assumed that the lung ELF-to-serum C_{max} ratio is 0.15 for REGN10933, REGN10987, and REGN10989. Dividing the target lung ELF concentration by this ratio, the associated serum concentration for these targets is therefore estimated to be ~at least 5 µg/mL for the combination of REGN10987+REGN10933, and ~0.1 µg/mL for REGN10989.

Taking into account uncertainties regarding mAb penetration into lung ELF, prediction of human PK, and effects of disease on PK, 20 µg/mL was selected as a target concentration in serum for the initial dose of REGN10933+REGN10987 combination therapy. The goal for the initial REGN10933+REGN10987 combination dose is for ≥95% of patients to exceed the target serum

concentration for 28 days after dosing, for each mAb. Based on healthy subject human PK data for six Regeneron mAbs directed against an exogenous target (N=6 to 12 subjects per mAb), a single IV combination dose of 1200 mg per mAb is predicted to result in ≥95% of patients exceeding the target serum concentration for 28 days after dosing, for each mAb.

*Please note that the EC values discussed here are identical to the inhibitory concentration (IC) values discussed in the Investigator's Brochure(s).

3.2.2.2. Phase 3 Dose Selection

Adult Patients

Note: A subset of patients in phase 3 were enrolled prior to the phase 3 adaptations implemented in protocol amendment 6 and received study drug doses selected for phase 1 and 2.

Phase 3 will assess 2 dose levels of REGN10933+REGN10987, 1200 mg and 2400 mg, administered in a 1:1 ratio (600 mg and 1200 mg per mAb, respectively). The 1:1 ratio for REGN10933+REGN10987 is thought to be appropriate as these are noncompeting mAbs targeting non-overlapping epitopes of the RBD of the S protein of SARS-CoV-2, with similar in vitro binding and neutralization properties (for more information, refer to the Investigator's Brochure). In the most recent analysis of phase 1 and 2 results in study R10933-10987-COV-2067, the 2400 mg and 8000 mg doses of REGN10933+REGN10987 demonstrated similar virologic and clinical efficacy as assessed by medically attended visits (MAVs), and both doses had similar and acceptable safety profiles. Given the similarities between the 2400 mg and 8000 mg doses, the 2400 mg dose will be studied in this phase 3 study as the highest dose, along with a lower dose of 1200 mg. Based on the observed linear PK for both mAbs, the 1200 mg dose is expected to provide 50% of the REGN10933 and REGN10987 exposures of the 2400 mg dose.

Pediatric Patients

Dose selection in the pediatric population (<18 years of age) utilized a body weight-tiered flat dose approach for both the higher and lower doses. For each weight-tiered dose targeting the higher dose in adults (2400 mg), the goal is to select doses that are predicted by population PK modeling to ensure that the lower fifth percentile of concentration in serum 28 days after dosing (C_{28}) is similar to, or greater than, the observed lower fifth percentile of C_{28} in adults for the 2400 mg dose. An additional consideration is to ensure that predicted C_{max} and $AUC_{0\text{-}28}$ for each weight-tiered dose do not exceed values previously achieved in adults. Although the 1200 mg dose has not been evaluated in adults, both REGN10933 and REGN10987 have demonstrated linear PK, and as such, the same 50% reduction employed in selecting the lower adult dose in phase 3 (2400 mg to 1200 mg) was applied to each of the pediatric body weight-tiered flat doses targeting the 1200 mg adult dose (Table 2).

To facilitate the predicted exposures in pediatric patients a 2-compartment population PK model with linear clearance developed for adults was used to simulate concentrations in serum over time for various doses in each pediatric weight group using allometrically scaled estimates of clearance and volume of distribution [gestational-age corrected allometrically scaled estimates were used for subjects <10 kg] (Robbie, 2012). For the pediatric doses in each weight group for the equivalent adult 2400 mg dose shown in Table 2, the predicted fifth percentile of C_{28} for all pediatric weight groups was greater than the observed fifth percentile of C_{28} for the adult 2400 mg dose; the predicted 50^{th} percentile of C_{28} for all pediatric weight groups ranged from 1.0 to 1.3x and 1.3 to

1.6x the observed 50th percentile of C_{28} for REGN10933 and REGN10987 for the adult 2400 mg dose, respectively. The predicted 95th percentiles of C_{max} and AUC_{0-28} for each pediatric dose equivalent of the 2400 mg adult dose were below the observed 50th percentiles of C_{max} and observed mean AUC_{0-28} values for both REGN10933 and REGN10987 for adults at 8000 mg, a dose shown to have an acceptable safety and tolerability profile.

3.3. Risk-Benefit

As described in Section 3.2.1.5, phase 1 and 2 data showed that treatment with REGN10933+REGN10987 reduced viral load and led to positive trends in clinical outcomes as demonstrated by significant reductions in COVID-19-related MAVs. These results were observed in the overall population of patients that were SARS-CoV-2 RT-qPCR positive at baseline, although it was more striking in individuals who had at least 1 pre-existing risk factor for severe COVID-19, were seronegative at baseline, or in those whose immune response was not sufficiently strong to reduce viral load as evidenced by high baseline viral loads. Treatment with REGN10933+REGN10987 was able to compensate for the absent or insufficient immune response and was able to reduce the mean viral load and decrease the number of MAVs. Overall, these data provide promising evidence for the use of REGN10933+REGN10987 in outpatients with SARS-CoV-2 infection.

These positive efficacy results are balanced by an acceptable safety profile. Nonclinical toxicology studies in nonhuman primates showed that REGN10933+REGN10987 was well-tolerated without adverse findings. Important identified risks, important potential risks, and other theoretical considerations are described below.

Important Identified Risks. As with other protein therapeutics, hypersensitivity reactions, including acute infusion-related reactions (intravenous [IV] administration) or injection site reactions (subcutaneous [SC] administration), may develop immediately or within a few hours to days after study drug administration. Hypersensitivity reactions, including infusion-related reactions or injection site reactions, have been observed in patients who received REGN10988+REGN10933 during ongoing clinical trials.

Important Potential Risks. The important potential risks of REGN10933+REGN10987 are the clinical consequences of immunogenicity and embryo-fetal toxicity.

Protein therapeutics carry the potential risk of an immunogenic response in the form of ADA and NAb development following administration, with possible consequences on safety and efficacy. Therefore, blood samples for immunogenicity assessment will be collected during the studies.

Reproductive and developmental toxicology studies have not been conducted; therefore, the effects of REGN10933, REGN10987, and REGN10933+REGN10987 combination therapy on the fetus and reproductive organs in males and females are unknown. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier and are present in breast milk; therefore, the REGN10933+REGN10987 combination therapy have the potential to be transferred from the mother to the developing fetus or a breastfed child. Given the high affinity and specificity of REGN10933 and REGN10987, off-target pharmacological effects are not anticipated in either the mother or the fetus, and no off-target binding of REGN10933 or REGN10987 was observed in any of the human or monkey tissues evaluated ex vivo in tissue cross-reactivity studies. However,

it is unknown whether the potential transfer of the combination of REGN10933+REGN10987 therapy provides any treatment benefit or risk to the developing fetus or a breastfed child.

There is currently limited clinical experience in the use of REGN10933, REGN10987, and REGN10933+REGN10987 combination therapy in female patients who are pregnant or breastfeeding. The combination of REGN10933+REGN10987 therapy should be used during pregnancy or breastfeeding only if the potential benefit justifies the potential risk for the mother and the fetus or breastfed child considering all associated health factors. If a female patient is pregnant or were to become pregnant while receiving REGN10933+REGN10987 combination, the pregnancy should be followed until outcome and any safety issue observed get reported.

Other Theoretical Considerations

Theoretical risks of administration of the REGN10933+REGN10987 combination include interference with the patient's endogenous immune response to either SARS-CoV-2 infection or vaccination against COVID-19. In this study, risk mitigation includes exclusion criteria for certain vaccination scenarios (refer to Section 7.2.2). A reference to current CDC guidance is provided (Section 8.10.1) to aid investigators on appropriate management of COVID-19 vaccination.

Antibody-dependent enhancement (ADE) has been observed for some therapeutics targeting exogenous viral proteins. For antibody therapies, ADE is thought to occur when binding of antibody to the target viral protein enhances Fc gamma receptor (FcγR)-mediated host cell entry of the virus (Iwasaki, 2020). This could potentially lead to worsening of disease and, in the case of SARS, acute lung injury (Liu, 2019). REGN10933 and REGN10987 retain the Fc region, as this may play a role in protecting against viral infection (Yasui, 2014), there is no strong evidence of ADE in other coronavirus models (Kam, 2007) (Liu, 2019) (Luo, 2018). To date, Fc-containing mAbs developed by the Sponsor for Ebola virus and MERS-CoV have demonstrated specificity to their exogenous targets with no significant unexpected safety findings in preclinical or clinical studies. All patients will have follow-up assessments by phone during the drug elimination period.

Pediatric Population. Emerging data suggest that the pediatric population is equally vulnerable to SARS-COV-2 infection, and may contribute significantly to viral transmission (Wang, 2016) (Weingartl, 2004). Moreover, neonatal transmission of SARS CoV-2 has also been reported, suggesting that the youngest of the pediatric population can also be at risk of infection (Lewis, 2020) (Szablewski, 2020). If infected, the burden of severe disease in pediatric patients that become symptomatic and develop COVID-19 seem to be greater in those with underlying medical conditions. As noted above, the current safety profile of REGN10933+REGN10987 is a marked by the absence of any identified safety signals. As it is an exogenous target, the safety of REGN10933+REGN10987 is not anticipated to be different from that observed in the adult patients. Additionally, nonclinical toxicology studies have not shown any safety findings including no tissue cross-reactivity to human fetal tissues. These data therefore favor assessing the safety and efficacy of REGN10933+REGN10987 in pediatric patients (for more information on dose rationale for these patients, refer to Section 3.2.2).

Summary. Overall, the anticipated benefit of REGN10933+REGN10987 combination therapy in treatment of infection with SARS-CoV-2 virus, along with the risk minimization measures in place, support clinical development of the product and the initiation and conduct of clinical trials.

For additional information, refer to the Investigator's Brochure.

4. ENDPOINTS

4.1. Primary Endpoints

The definition of a COVID-19-related medically-attended visit is provided in Section 9.2.3.2. Note that a patient with multiple COVID-19 related MAVs will be counted as having one event.

Phase 1

The primary endpoints for phase 1 are:

- Proportion of patients with treatment-emergent serious adverse events (SAEs) through day 29
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29
- Time-weighted average change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7, as measured by RT-qPCR in NP swab samples.

  Note: Time-weighted average of change from baseline viral load from day 1 to day 7 will be calculated for each patient using the trapezoidal rule as the area under the curve for change from baseline at each time point divided by the time interval for the observation period.

Phase 2

The primary endpoint for phase 2 is time-weighted average change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7, as measured by RT-qPCR in NP swab samples.

Phase 3

Cohort 1

The primary endpoint for phase 3 is proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29.

Cohort 2

The primary endpoints for phase 3 are:

- Proportion of patients with treatment-emergent serious adverse events through day 29
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29
- Concentrations of REGN10933 and REGN10987 in serum over time

Cohort 3

The primary endpoints for phase 3 are:

- Proportion of patients with treatment-emergent serious adverse events through day 29
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29

4.2. Secondary Endpoints

The definition of a COVID-19-related medically-attended visit is provided in Section 9.2.3.2. Note that a patient with multiple COVID-19 related MAVs will be counted as having one event.

Phase 1

Virologic

- Time-weighted average change from baseline in viral load (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in saliva samples
- Time-weighted average change from baseline in viral load (log_{10} copies/mL) from day 1 to day 22, as measured by RT-qPCR in nasal swab samples
- Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples (nasopharyngeal swabs, nasal swabs, saliva)
- Change from baseline in viral load at each visit through day 29, as measured by RT-qPCR in nasopharyngeal swabs
- Change from baseline in viral load at each visit through day 29, as measured by RT-qPCR in saliva samples
- Change from baseline in viral load at each visit through day 29, as measured by RT-qPCR in nasal swabs
- Correlation and concordance of RT-qPCR results across different sample types (NP, nasal, and saliva)
- Time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 to post-baseline study days (eg, day 5, 7, 15, and 29)

Clinical

- Proportion of patients with ≥1 COVID-19-related medically-attended visit through day 29
- Proportion of patients with ≥2 COVID-19-related medically-attended visits through day 29
- Total number of COVID-19-related medically-attended visits through day 29
- Proportion of patients admitted to a hospital due to COVID-19 by day 29
- Proportion of patients with ≥1 outpatient or telemedicine visit due to COVID-19 by day 29

PK/ADA

- Concentrations of REGN10933 and REGN10987 in serum and corresponding pharmacokinetics parameters
- Immunogenicity, as measured by anti-drug antibodies to REGN10933 and REGN10987

Phase 2

The secondary endpoints for phase 2 are:

Virologic

- Time to negative RT-qPCR in nasopharyngeal swabs with no subsequent positive RT-qPCR
- Change from baseline in viral load at each visit, as measured by RT-qPCR in nasopharyngeal samples
- Time-weighted average change from baseline in viral load (log_{10} copies/mL) from day 1 to post-baseline study days
- Proportion of patients with high viral load ($>10^4$ copies/mL, $>10^5$ copies/mL, $>10^6$ copies/mL, $>10^7$ copies/mL) at each visit
- Proportion of patients with viral loads below the limit of detection at each visit
- Proportion of patients with viral loads below the lower limit of quantitation at each visit

Clinical

- Proportion of patients with ≥1 COVID-19-related medically-attended visit through day 29
- Proportion of patients with ≥2 COVID-19-related medically-attended visits through day 29
- Total number of COVID-19-related medically-attended visits through day 29
- Proportion of patients admitted to a hospital due to COVID-19 by day 29
- Proportion of patients admitted to an intensive care unit due to COVID-19 by day 29
- Proportion of patients with ≥1 outpatient or telemedicine visit due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29
- Days of hospitalization due to COVID-19
- Proportion of patients with all-cause mortality by day 29
- Time to first onset of symptoms consistent with COVID-19 (asymptomatic cohort only)
- Duration of symptoms consistent with COVID-19

Safety

- Proportion of patients with treatment-emergent serious adverse events through day 29
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29

PK/ADA

- Concentrations of REGN10933 and REGN10987 in serum
- Immunogenicity, as measured by anti-drug antibodies and neutralizing antibodies to REGN10933 and REGN10987

Phase 3

Cohort 1

The key secondary endpoints for phase 3 are:

- Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 through day 29
- Time to COVID-19 symptoms resolution.

Note: COVID-19 symptoms resolution is defined in Section 11.4.3.2.

The other secondary endpoints for phase 3 are:

Clinical

- Proportion of patients with ≥1 COVID-19-related hospitalization, emergency room visit, or all-cause death through day 29
- Proportion of patients with ≥1 COVID-19-related medically-attended visit or all-cause death through day 29
- Proportion of patients with ≥1 COVID-19-related medically-attended visit by type of visit (hospitalization, emergency room, urgent care, and/or physician's office/telemedicine) through day 29
- Proportion of patients with ≥2 COVID-19-related medically-attended visits through day 29
- Cumulative incidence of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29
- Cumulative incidence of patients with ≥1 COVID-19-related hospitalization, emergency room visit, or all-cause death through day 29
- Cumulative incidence of patients with ≥1 COVID-19-related medically-attended visit or all-cause death through day 29
- Days of hospitalization due to COVID-19
- Proportion of patients admitted to an intensive care unit due to COVID-19 by day 29
- Proportion of patients requiring supplemental oxygen due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29
- Total number of COVID-19-related medically-attended visits through day 29
- Time to all-cause death
- All-cause death by day 29, day 120, and day 169

Virologic

- Time-weighted average change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7, as measured by RT-qPCR in nasopharyngeal swab samples (patients enrolled prior to protocol amendment 6 only)
- Change from baseline in viral load at each visit, as measured by RT-qPCR in nasopharyngeal swab samples

Safety

- Proportion of patients with treatment-emergent serious adverse events through day 29
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29

PK/ADA

- Concentrations of REGN10933 and REGN10987 in serum
- Immunogenicity, as measured by anti-drug antibodies and neutralizing antibodies to REGN10933 and REGN10987

Cohort 2

The secondary endpoints for phase 3 are:

Clinical

- Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29
- Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 through day 29
- Proportion of patients with ≥1 COVID-19-related hospitalization, emergency room visit, or all-cause death through day 29
- Proportion of patients with ≥1 COVID-19-related medically-attended visit or all-cause death through day 29
- Proportion of patients with ≥1 COVID-19-related medically-attended visit by type of visit(s) (hospitalization, emergency room, urgent care, and/or physician's office/telemedicine) through day 29
- Proportion of patients with ≥2 COVID-19-related medically-attended visits through day 29
- Cumulative incidence of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29
- Cumulative incidence of patients with ≥1 COVID-19-related hospitalization, emergency room visit, or all-cause death through day 29
- Cumulative incidence of patients with ≥1 COVID-19-related medically-attended visit or all-cause death through day 29

- Days of hospitalization due to COVID-19
- Proportion of patients admitted to an intensive care unit due to COVID-19 by day 29
- Proportion of patients requiring supplemental oxygen due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29
- Total number of COVID-19-related medically-attended visits through day 29
- Time to all-cause death
- All-cause death by day 29, day 120, and day 169

Virologic

- Time-weighted average change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7, as measured by RT-qPCR in nasopharyngeal swab samples
- Change from baseline in viral load at each visit, as measured by RT-qPCR in nasopharyngeal swab samples

ADA

- Immunogenicity, as measured by anti-drug antibodies and neutralizing antibodies to REGN10933 and REGN10987

Cohort 3

The secondary endpoints for phase 3 are:

PK/ADA

- Concentrations of REGN10933 and REGN10987 in serum over time
- Immunogenicity, as measured by anti-drug antibodies and neutralizing antibodies to REGN10933 and REGN10987

4.3. Exploratory Endpoints

The exploratory endpoints for phase 1 and phase 2:

- Change and percentage change in neutrophil-lymphocyte ratio (NLR) at each visit through day 29
- Change and percentage change in D-dimer at each visit through day 29
- Change and percentage change in ferritin at each visit through day 29
- Change and percentage change in C-reactive protein (CRP) at each visit through day 29
- Change and percentage change in lactate dehydrogenase (LDH) at each visit through day 29
- Change in SE-C19 item scores over time
- Change in PGIS score over time
- PGIC score at day 29

Additional exploratory endpoints for phase 1 only:

- Proportion of patients admitted to an intensive care unit due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29

Phase 3

The exploratory endpoints for phase 3 are:

- Viral load over time in patients with and without COVID-19-related medically-attended visits
- Change in WPAI+CIQ over time
- Change in EQ-5D-5L over time
- Time to COVID-19 symptoms resolution (cohort 2 ages ≥12 years)

Note: COVID-19 symptoms resolution is defined in Section 11.4.3.2.

5. STUDY VARIABLES

This section outlines variables to be measured in the study. For description and rationale of corresponding study procedures, refer to Section 9.2. For a full listing of variables, refer to the corresponding statistical analysis plans.

5.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, etc), disease characteristics, medical history, risk factors for severe COVID-19, and medication history for each patient.

5.2. Efficacy Variables

Efficacy variables include viral load (log_{10} copies/mL), number of patients with a COVID-19-related medically-attended visit, number of patients admitted to a hospital, ICU, or outpatient telemedicine visit, and number of patients requiring mechanical ventilation.

5.3. Safety Variables

Safety variables include incidence of targeted TEAEs as described in Section 10.1.1.

5.4. Pharmacokinetic Variables

For phase 1, the PK variables are the concentration of REGN10933 and REGN10987 in serum and time and select PK parameters. For phase 2 and phase 3, the variables are the concentration of REGN10933 and REGN10987 in serum and time. Samples will be collected at the visits specified in the relevant schedule of events.

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, NAb positivity (yes/no), and time point/visit. Samples will be collected at the visits specified in the relevant schedule of events.

5.6. Pharmacodynamic and Other Biomarker Variables

Exploratory endpoint variables may include, but not be limited to, parameters reported in complete blood counts with differential, levels of D-dimer, ferritin, CRP, LDH, cardiac biomarkers, per-symptom SE-C19 score, PGIS score, and PGIC score.

These results may be reported outside of the clinical study report (CSR).

6. STUDY DESIGN

6.1. Study Description and Duration

This is an adaptive, phase 1/2/3, randomized, double-blinded, placebo-controlled master protocol to evaluate the efficacy, safety, and tolerability of REGN10933+REGN10987 combination therapy in ambulatory patients (ie, outpatients) with COVID-19, including (in phase 2) asymptomatic patients with SARS-CoV-2 infection. The study will be conducted in approximately 120 sites, in the US and other countries. To be eligible, patients must have laboratory-confirmed SARS-CoV-2 but must not have been previously hospitalized for COVID-19 or currently hospitalized for any reason. In phase 1, only patients with COVID-19 symptoms will be enrolled. In phase 2, symptomatic patients and asymptomatic patients will be enrolled into separate cohorts. In phase 3, symptomatic patients who are ≥18 years old and <18 years old, and not pregnant at randomization, will be enrolled in two separate cohorts. Patients who are pregnant at randomization, regardless of age, will be enrolled in a third cohort (refer to Section 7.2 for study inclusion and exclusion criteria).

The schedule of events can be found in Table 3 (phase 1), Table 4 (phase 2), Table 5 (phase 3, cohort 1; phase 3, cohort 3 patients ≥18 years), and Table 6 (phase 3, cohort 2; phase 3, cohort 3 patients <18 years). See Figure 2 (phase 1), Figure 3 (phase 2), 4 (phase 3, cohort 1), and Figure 5 (phase 3, cohort 2) for study flow diagrams. Additional information on study procedures can be found in Section 9.2.

6.1.1. Phase 1

Note: As of protocol amendment 6, phase 1 has been completed and is closed.

On day 1, eligible patients will be randomized to a single intravenous (IV) administration of REGN10933+REGN10987 (2400 mg), REGN10933+REGN10987 (8000 mg), or placebo. Patients will also have NP swab, nasal swab, and saliva samples taken and have blood drawn for safety, PK, ADA, and exploratory analyses.

Patients in the phase 1 sentinel safety group (Section 3.2.1.1) will be sequestered for the first 48 hours after dosing, during which time they will be closely monitored for TEAEs (grade 3 or 4), treatment-emergent SAEs, and treatment-emergent AESIs (Section 10). This sequester period is mandatory. These patients will then have the option to leave their sequester on day 3 (if medically appropriate) after completing day 3 assessments. Alternatively, patients may choose to remain sequestered for any additional period of time up to day 7. After completing assessments on day 7, all patients who are still sequestered will be sent home, if medically appropriate.

Patients who are not in the sentinel safety group will not have a mandatory sequestering period. However, they will have the option to be sequestered for any period of time up to day 7. After completing assessments on day 7, all patients who are still sequestered will be sent home, if medically appropriate.

Since patients will be sequestered and/or home for the duration of the study, assessments and sample collections may occur through a variety of in-person and remote methods. This may include (but is not limited to) visits at the study site or place of infusion, visits at the place of sequester, home-based visits (defined as visits by home health staff, at mobile units, and/or testing centers), or by phone/telemedicine. Throughout the study, biological samples will be obtained by study

personnel only at study locations where appropriate personal protective equipment (PPE) can be used.

NP swabs, nasal swabs, and saliva samples will be collected every other day for the first 2 weeks and then approximately twice weekly thereafter. Patients will also have blood drawn during a subset of these visits.

Information regarding SAEs, AESIs, and medically-attended related due to COVID-19 will be recorded during weekly telemedicine and/or phone visits, and patients will be asked to notify study personnel as soon as possible about any medically-attended visits. Throughout the study, patients will also provide daily self-reported information about COVID-19 symptoms through an electronic survey.

The study will end on day 29, when patients will have final assessments including NP swab, nasal swab, and saliva sample collections and blood draws for PK, ADA, and exploratory analyses.

6.1.2. Phase 2

Note: As of protocol amendment 6, phase 2 has been completed and is closed.

Phase 2 will initiate following IDMC clearance of a pooled phase 1 sentinel safety group across 2 studies (R10933-10987-COV-2066 and R10933-10987-COV-2067), and after initiation will enroll concurrently with phase 1. Once phase 2 is active, phase 1 will continue to enroll to completion, but phase 2 enrollment does not require the completion of phase 1 enrollment (for complete description and rationale for this process, refer to Section 3.2.1).

On day 1, eligible patients will be randomized 1:1:1 to a single dose of REGN10933+REGN10987 (2400 mg), REGN10933+REGN10987 (8000 mg), or placebo. Patients will also have NP swabs taken and blood drawn for safety, PK, ADA, and exploratory analyses.

Patients will not be sequestered during phase 2. After infusion of study drug, patients will be observed for 2 hours and, if no SAEs or AESIs are observed, will be sent home (if medically appropriate).

Since patients will be at home, subsequent assessments and sample collections will potentially occur through a variety of in-person and remote methods as described in phase 1. NP swabs will be collected every other day for the first 2 weeks and then approximately twice weekly thereafter. Blood samples will also be collected periodically.

Information regarding treatment-emergent SAEs, treatment-emergent AESIs, and medically-attended visits related to COVID-19 will be recorded during weekly telemedicine and/or phone visits, and patients will be asked to notify study personnel as soon as possible about any medically-attended visits. Throughout the study, patients will also provide daily self-reported information about COVID-19 symptoms through an electronic survey.

On day 29, patients will have final assessments including NP swab collection and blood draws for PK, ADA, and exploratory analysis.

All patients in phase 2, regardless of cohort, will follow the same schedule of events.

6.1.3. Phase 3

In phase 3, eligible patients in cohort 1 and cohort 2 will be randomized 1:1:1 to a single dose of placebo or one of two dose levels of REGN10933+REGN10987. In cohort 1, REGN10933+REGN10987 dose levels will consist of 1200 mg and 2400 mg. In cohort 2, body-weight equivalents of these two dose levels will be used. Patients in cohort 3 will be randomized 1:1 to one of two dose levels of REGN10933+REGN10987 (ie, no randomization to placebo), at 1200 mg and 2400 mg or body-weight equivalents as applicable.

Note that as of 25 February 2021 (per IDMC recommendation and subsequently formalized in protocol amendment 8), patients will no longer be randomized to placebo (Section 8.6).

On the day of dosing, patients will have NP swabs taken for SARS-CoV-2 RT-qPCR testing and blood drawn for safety, drug concentration, immunogenicity, and exploratory analyses. After infusion, patients will be monitored for at least 1 hour and released from the study site, if medically appropriate. Patients <12 years of age will be monitored for at least 2 hours after infusion, with more frequent vital sign assessments (refer to schedules of events for more information).

Targeted safety information (Section 10.1.1) and COVID-19-related medically-attended visit details (Section 9.2.3.2) will be collected on an ongoing basis; minimally, patients (or their caregivers) will be queried during weekly phone visits through the first 29 days of the study. For patients <12 years of age, a phone call will be made within 6 to 8 hours after completing the infusion to collect targeted safety information; these patients (or their caregivers) should be instructed to contact the site within 24 hours post-infusion if they experience any side effects. Patients (or their caregivers) will also be asked to notify study personnel as soon as possible about any unplanned medically-attended visits that occur during the study.

Assessments and sample collections may potentially occur through a variety of in-person and remote methods. This may include (but is not limited to) visits at the study site or place of infusion, home-based visits (defined as visits by home health staff, at mobile units, and/or testing centers), or by phone/telemedicine. Throughout the study, biological samples will be obtained by study personnel only at study locations where appropriate PPE can be used.

Patients enrolled in cohort 1 will follow the schedule events in Table 5. These patients will have NP swabs and blood samples collected approximately every week through day 29 and will provide self-reported information about COVID-19 symptoms through electronic surveys (both daily and weekly). A subset of patients in cohort 1 will be enrolled in a PK sub-study (Section 9.2.8). [redacted]

Patients enrolled in cohort 2 will follow the schedule events in Table 6. These patients will also have NP swabs and blood samples collected approximately every week through day 29, with an NP swab additionally collected on day 3. To reduce overall patient burden of blood sampling in this younger cohort, the frequency of blood sample collection and the total amount of blood collected per visit will vary according to body weight. In addition, patients in this cohort will be randomly assigned to one of four staggered PK-ADA sampling schedules. This will be done according to a central randomization scheme using an interactive web response system (IWRS).

Patients enrolled in cohort 3 will follow the schedule of events for either cohort 1 or cohort 2, depending on the age of the enrollee at randomization. Patients who meet the age criteria for cohort 1 at randomization will follow Table 5; those who meet the age criteria for cohort 2 at randomization will follow Table 6. Refer to Section 7.2 for age criteria. Note that Table 5 includes additional drug concentration and immunogenicity samples for patients enrolled in cohort 3.

After the final in-person visit, all cohorts will have 2 follow-up phone calls to collect safety information, including (when applicable) additional information regarding pregnancy outcome (Section 9.2.5).

Enrollment of Phase 3 Participants Prior to Phase 3 Adaptations

Note that a subset of patients in phase 3 were enrolled prior to the phase 3 adaptations implemented in protocol amendment 6. Patients enrolled prior to protocol amendment 6 followed the schedule of events in Table 4, which included a more intensive regimen of NP swab sample collection. These patients will be re-consented and will follow the phase 3 schedule of events in Table 5 beginning at the point at which they re-consent. Data from these patients may be subject to modified and/or additional analyses, contingent upon sample collection frequency, eligibility with inclusion/exclusion criteria adaptation, and other parameters. Additional information will be provided in the statistical analysis plan.

Sharing of Data Across Studies

For patients in this study who are also index cases of household contacts in the R10933-10987-COV-2069 prophylaxis study, data may be used from R10933-10987-COV-2067 as part of R10933-10987-COV-2069 analyses. The data may include treatment arm allocation, virologic and serologic data and treatment outcomes. This will facilitate, in R10933-10987-COV-2069, assessing the potential impact of REGN10933+REGN10987 treatment of index cases on infection rates in household contacts.

Figure 2: Study Flow Diagram, Phase 1

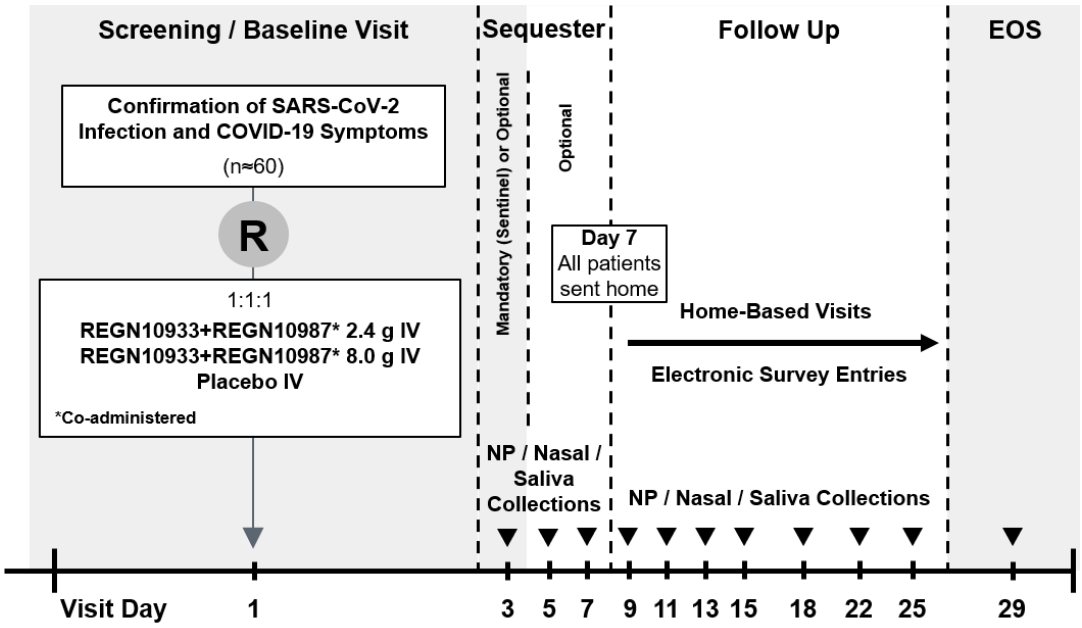


Figure 3: Study Flow Diagram, Phase 2 (and Phase 3 Prior to Amendment 6)

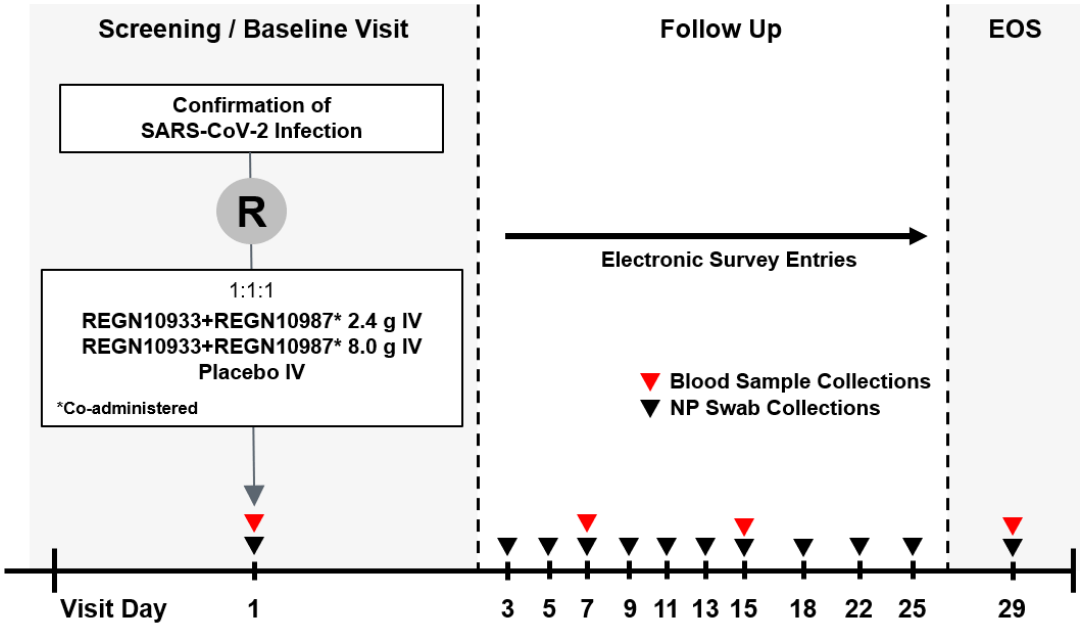


Figure 4: Study Flow Diagram, Phase 3 (Cohort 1 Patients; Cohort 3 Patients ≥18 Years)

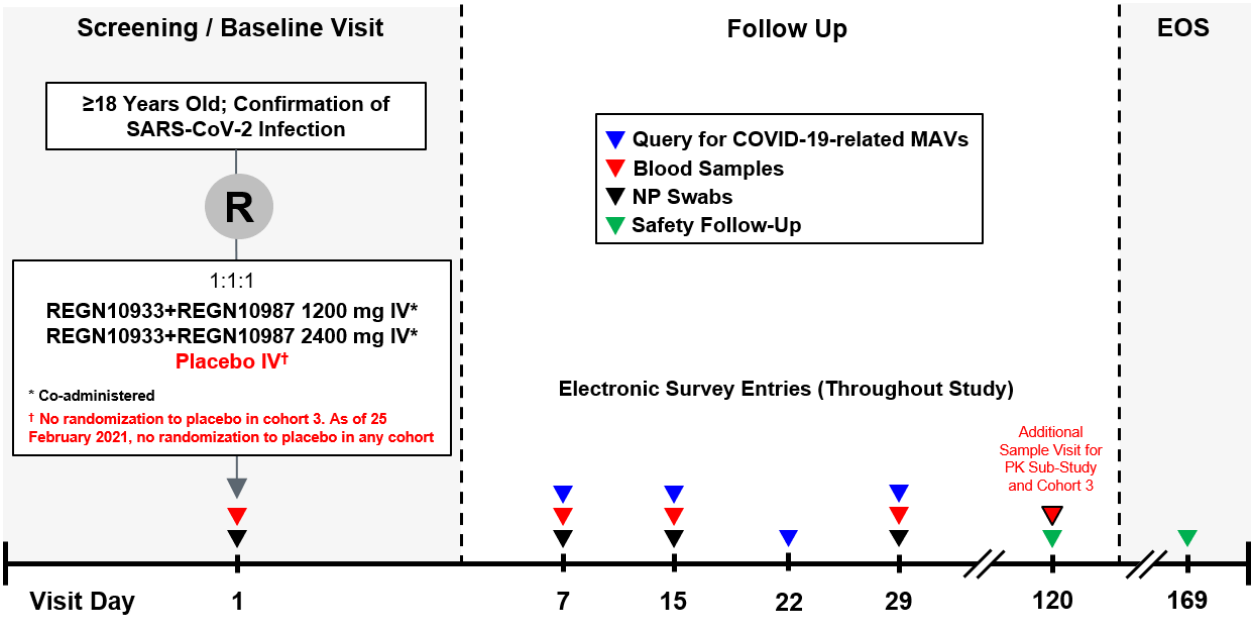
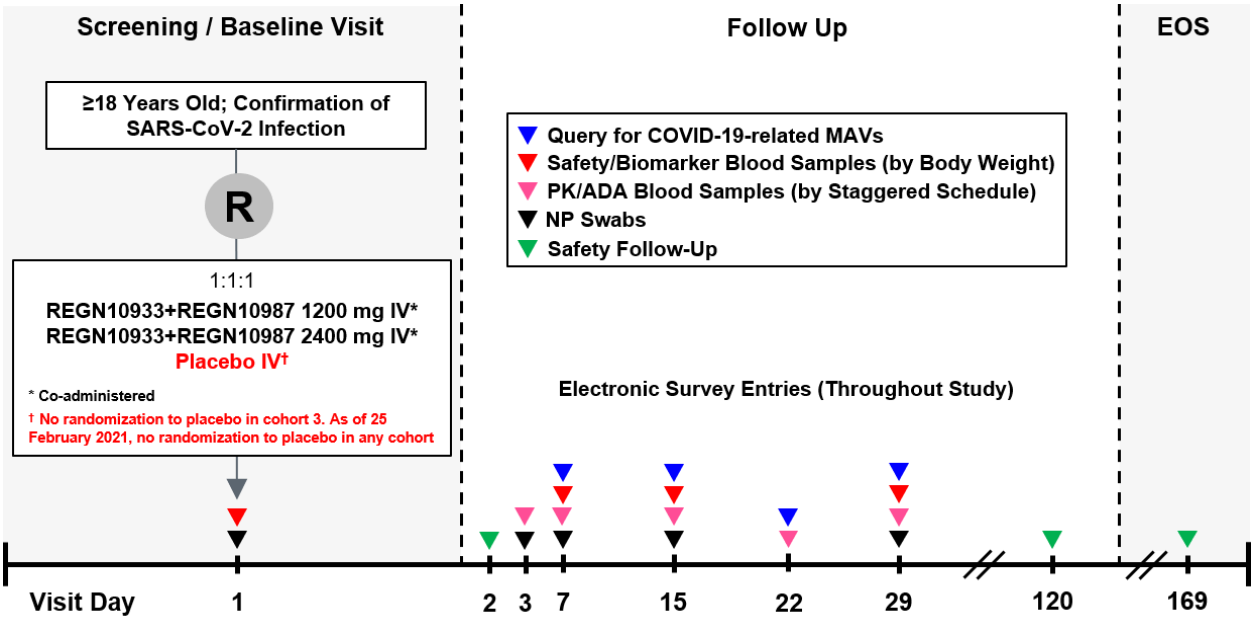


Figure 5: Study Flow Diagram, Phase 3 (Cohort 2 Patients; Cohort 3 Patients <18 Years)



6.1.4. Study Stopping Rules

6.1.4.1. Individual Patient Stopping Rules

For an individual patient, the infusion rate can be slowed, interrupted, or stopped if there is a suspected drug-related event during the infusion suggestive of severe hypersensitivity or an infusion-related reaction, as per investigator discretion if it is deemed to be in the patient's best interest (see Section 8.5). As this is a single dose study, there are no other study drug discontinuation rules.

Patient stopping rules from the study include withdrawal of consent.

6.1.4.2. Study Stopping Criteria

The Sponsor may decide to stop or make adaptations to the study based upon the recommendations by an IDMC recommendations and/or review of the totality of evidence (see Section 6.2.1).

A treatment arm may be dropped if there is a clinically meaningful imbalance between treatment arms in both of the following criteria:

- Incidence of treatment-emergent SAEs evaluated as related to study treatment

  and

- A risk-benefit imbalance based upon any key efficacy and safety endpoint of the study such that one dosing arm appears to be doing substantially better than another without requiring any specific statistical level of precision

6.1.5. End of Study Definition

The end of study is defined as the date when the last living patient completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).

6.2. Study Committees

6.2.1. Independent Data Monitoring Committee

An IDMC will actively review data throughout the study to monitor patient safety and efficacy data. The IDMC can make recommendations about early study closure or changes to the study conduct. The operation of the IDMC is governed by a charter describing further details, such as procedures (including but not limited to periodic safety monitoring) and requirements for reporting its observations to the Sponsor.

An IDMC will review pooled safety data through day 3 in the sentinel safety group as described in Section 3.2.1. In addition, the IDMC will conduct periodic data reviews, for instance, after all patients are enrolled into phase 1. Additional periodic reviews will be conducted during phase 2 and 3 of this study as detailed in the IDMC charter. These data reviews will include all available efficacy and safety data, including deaths, from all enrolled study participants up to the data cut point for the analysis. The IDMC will meet regularly throughout the course of the study to review safety data and make recommendations on study conduct.

6.2.2. Sponsor Review Committee

Periodic data reviews may be performed by selected unblinded senior Sponsor physicians and a statistician with no direct involvement in the study. Reviews will assess the totality of evidence and may be used to determine study adaptations (see Section 3.2.1.2).

6.3. Planned Interim Analysis

A description of the statistical methods to be employed is provided in Section 11.5, and blinding implications are discussed in Section 8.7.

Initial Phase 1/2

An interim descriptive analysis of first 275 symptomatic randomized patients was planned.

Phase 3

An interim analysis may be performed in phase 3. Refer to Section 11.4.4 and Section 11.5 for details regarding this analysis.

6.4. Periodic Data Reviews

Periodic reviews may be performed during phase 1 and phase 2 by selected unblinded senior Sponsor physicians and a statistician with no direct involvement in the study. Reviews will assess the totality of evidence and in phase 2 may be used to determine study adaptations (eg, whether to drop a dose arm).

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

Phase 1 will continue to enroll until approximately 100 patients are randomized. Phase 2 will continue to enroll until approximately 1300 patients are randomized.

It is estimated that up to approximately 8500 patients will be required for phase 3 cohort 1. For cohort 2, it is estimated that up to approximately 180 patients will be required. This will include minimum enrollment according to weight categories (refer to Section 8.6).

For information on the initial timing of enrollment for phase 1 and phase 2, refer to Section 3.2.1. For treatment allocation and randomization, refer to Section 8.6. Additional information on sample size can be found in Section 11.2.

7.2. Study Population

This study will enroll non-hospitalized patients who have a positive diagnostic test for SARS-CoV-2.

7.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Meets 1 of the following 3 criteria:
   a. **Cohort 1**: ≥18 years of age and not pregnant at randomization
   b. **Cohort 2**: <18 years of age and not pregnant at randomization
   c. **Cohort 3**: Pregnant at randomization
   Note: cohort 2 and cohort 3 will only be enrolled where permitted by local requirements
2. Has SARS-CoV-2-positive diagnostic test from a sample collected ≤72 hours prior to randomization, using a validated SARS-CoV-2 antigen, RT-PCR, or other molecular diagnostic assay and an appropriate sample such as nasopharyngeal [NP], nasal, oropharyngeal [OP], or saliva

   Note: Historical record of positive result is acceptable, as long as the sample was collected ≤72 hours prior to randomization.
3. [Criterion removed]
4. Has symptoms consistent with COVID-19, as determined by the investigator, with onset ≤7 days before randomization
5. Maintains O_2 saturation ≥93% on room air
6. Is willing and able to provide informed consent as below:
   a. If at or above country's legal age of adulthood, signed by study patient or legally authorized representative
   b. If below country's legal age of adulthood, signed by parent(s) or legal guardian(s).

Age-appropriate assent will be collected from the study patient according to local regulatory (competent authority/ethics) guidelines

7. Is willing and able to comply with study procedures
8. Is able to understand and complete study-related questionnaires (patients aged ≥12 years only)
9. **Cohort 1 and Cohort 2 only:** has ≥1 risk factor for severe COVID-19

   Risk factors are defined as follows:

   a. Age ≥50 years **(cohort 1 only)**
   b. Obesity, defined as:
      BMI ≥30 kg/m^2 **(cohort 1 only)**
      BMI (kg/m2) ≥95th percentile for age and sex based on CDC growth charts **(cohort 2 ≥2 years only)**
   c. Cardiovascular disease, including hypertension
   d. Chronic lung disease, including asthma
   e. Type 1 or type 2 diabetes mellitus
   f. Chronic kidney disease, including those on dialysis
   g. Chronic liver disease
   h. [Risk factor removed]
   i. Immunosuppressed, based on investigator's assessment
      Examples include cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anemia, thalassemia, and prolonged use of immune-weakening medications
   j. Any underlying genetic condition, neurologic condition, metabolic condition, or congenital heart disease deemed by the investigator to be a risk factor for severe COVID-19 **(cohort 2 only)**

7.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Was admitted to a hospital for COVID-19 prior to randomization, or is hospitalized (inpatient) for any reason at randomization
2. Has participated, or is participating, in a clinical research study evaluating COVID-19 convalescent plasma, mAbs against SARS-CoV-2 (eg, bamlanivimab), or intravenous immunoglobulin (IVIG) within 3 months or within 5 half-lives of the investigational product (whichever is longer) prior to the screening visit
3. Prior, current, or planned future use of any of the following treatments: COVID-19 convalescent plasma, mAbs against SARS-CoV-2 (eg, bamlanivimab), IVIG (any indication), systemic corticosteroids (any indication), or COVID-19 treatments (authorized, approved, or investigational)

   Note: Prior use is defined as the past 30 days or within 5 half-lives of the investigational product (whichever is longer) from screening
4. *[Criterion consolidated with criterion #3]*

5. *[Criterion removed]*
6. Has known allergy or hypersensitivity to components of study drug
7. Has been discharged, or is planned to be discharged, to a quarantine center
8. *[Criterion removed]*
9. *[Criterion removed]*
10. Has a known positive SARS-CoV-2 serologic test
11. Has a positive SARS-CoV-2 antigen or molecular diagnostic test from a sample collected >72 hours prior to randomization
12. Has known active infection with influenza or other non-SARS-CoV-2 respiratory pathogen, confirmed by a diagnostic test
13. Prior use (prior to randomization), current use (at randomization), or planned use (within 90 days of study drug administration or per current CDC recommendations, as applicable) of any authorized or approved vaccine for COVID-19
14. Has participated, is participating, or plans to participate in a clinical research study evaluating any authorized, approved, or investigational vaccine for COVID-19
15. Is a member of the clinical site study team or their immediate family member

7.3. Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or Sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patient who are withdrawn prematurely from the study will be asked to complete an early termination visit and follow up contact, as described in Section 1.

7.4. Replacement of Patients

In phase 1, patients who have missing or negative baseline virologic sample(s) or are missing ≥1 follow-up virologic sample(s) may be replaced. Patients prematurely discontinued from the study will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

Instructions on dose preparation are provided in the pharmacy manual. See Section 8.6 for dose levels and method of treatment allocation for each phase of the study.

- Co-administered REGN10933+REGN10987 combination therapy
- Placebo IV single dose

8.2. Background Treatment

No background treatment will be allowed. Patients may self-administer non-prescribed medications (eg, antipyretics).

8.3. Rescue Treatment(s)

Patients can receive rescue therapy for COVID-19 per local standard-of-care. Rescue treatment(s) will not be provided as part of the study.

8.4. Dose Modification and Study Treatment Discontinuation Rules

8.4.1. Dose Modification

This is a single dose study; dose modification is not allowed.

8.4.2. Study Drug Discontinuation

This is a single dose study; study drug discontinuation is not applicable.

8.5. Management of Acute Reactions

8.5.1. Infusion-Related Reactions and Hypersensitivity Reactions

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use if required for treatment. All grade ≥2 infusion-related reactions and grade ≥2 hypersensitivity reactions (using the CTCAE severity scale specified in Section 10.2.5) must be reported as AESIs (see Section 10.2.3).

8.5.1.1. Interruption of the Intravenous Infusion

The infusion should be interrupted if any of the following AEs are observed:

- Sustained/severe cough
- Rigors/chills
- Rash, pruritus (itching)
- Urticaria (hives, welts, wheals)
- Diaphoresis (sweating)
- Hypotension
- Dyspnea (shortness of breath)
- Vomiting
- Flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate.

If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

8.5.1.2. Termination of the Intravenous Infusion

The infusion should be terminated and **not** restarted if any of the following AEs occur:

- Anaphylaxis*
- Laryngeal/pharyngeal edema
- Severe bronchospasm
- Chest pain
- Seizure
- Severe hypotension
- Other neurological symptoms (confusion, loss of consciousness, paresthesia, paralysis, etc)
- Any other symptom or sign that, in the opinion of the investigator, warrants termination of the IV infusion

*Consider anaphylaxis if the following is observed (Sampson, 2006): acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) **and at least one of the following:**

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

8.6. Method of Treatment Assignment

Patients will be randomized according to a central randomization scheme using an interactive web response system (IWRS).

Phase 1

Patients will be randomized in a 1:1:1 allocation ratio to one of the following:

- Co-administered REGN10933+REGN10987 combination therapy, 2400 mg (1200 mg each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 8000 mg (4000 mg each of REGN10933 and REGN10987) IV single dose
- Placebo IV single dose

In phase 1, randomization will not be stratified.

Phase 2 (and Phase 3 Prior to Protocol Amendment 6)

Patients will be randomized in a 1:1:1 allocation ratio to one of the treatments listed below:

- Co-administered REGN10933+REGN10987 combination therapy, 2400 mg (1200 mg each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 8000 mg (4000 mg each of REGN10933 and REGN10987) IV single dose
- Placebo IV single dose

In phase 2, randomization will be stratified by:

- Presence/absence of COVID-19 symptoms (ie, symptomatic versus asymptomatic cohort)
- Country
- Risk factors for hospitalization due to COVID-19 (no risk factors for hospitalization due to COVID 19 versus ≥1 risk factor for hospitalization due to COVID-19)

The following are considered risk factors for the purposes of stratification (for rationale, refer to Section 3.2.1.5):

- Age >50 years
- Obesity, defined as BMI >30
- Cardiovascular disease, including hypertension
- Chronic lung disease, including asthma
- Chronic metabolic disease, including diabetes
- Chronic kidney disease, including those on dialysis
- Chronic liver disease
- Immunosuppressed, based on investigator's assessment (examples include: cancer treatment, bone marrow or organ transplantation, immune deficiencies, poorly-controlled HIV or AIDS, and prolonged use of immune-weakening medications)

Phase 3

Cohort 1 (Prior to 25 February 2021)

Patients in cohort 1 who are enrolled into phase 3 under protocol amendment 6 or 7 will be randomized in a 1:1:1 allocation ratio to one of the treatments listed below:

- Co-administered REGN10933+REGN10987 combination therapy, 1200 mg (600 mg each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 2400 mg (1200 mg each of REGN10933 and REGN10987) IV single dose
- Placebo IV single dose

In phase 3 cohort 1, Randomization will be stratified by country.

Cohort 1 (25 February 2021 and Later)

Patients in cohort 1 who are enrolled into phase 3 under protocol amendment 8 or later will be randomized in a 1:1 allocation ratio to one of the treatments listed below:

- Co-administered REGN10933+REGN10987 combination therapy, 1200 mg (600 mg each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 2400 mg (1200 mg each of REGN10933 and REGN10987) IV single dose

In phase 3 cohort 1, randomization will be stratified by country.

Cohort 2 (Prior to 25 February 2021)

Patients in cohort 2 will be randomized in a 1:1:1 allocation ratio to co-administered REGN10933+REGN10987 combination therapy, IV single dose at 1200 mg (or body weight equivalent), 2400 mg (or body weight equivalent), or placebo. The REGN10933+REGN10987 dose level will be adjusted according to body weight as defined in Table 2.

In phase 3 cohort 2, randomization will be stratified by country.

Table 2: REGN10933+REGN10987 IV Doses for Each Weight Group, Phase 3 Cohort 2 (Ages 0 to <18 Years)

Body Weight Group	Dose Equivalent for REGN10933+REGN10987 1200 mg IV Dose (600 mg per mAb)	Dose Equivalent for REGN10933+REGN10987 2400 mg IV Dose (1200 mg per mAb)
≥40 kg	1200 mg (600 mg per mAb)	2400 mg (1200 mg per mAb)
≥20 kg to <40 kg	450 mg (225 mg per mAb)	900 mg (450 mg per mAb)
≥10 kg to <20 kg	224 mg (112 mg per mAb)	450 mg (225 mg per mAb)
≥5 kg to <10 kg	120 mg (60 mg per mAb)	240 mg (120 mg per mAb)
≥2.5 kg to <5 kg	60 mg (30 mg per mAb)	120 mg (60 mg per mAb)
<2.5 kg	30 mg (15 mg per mAb)	60 mg (30 mg per mAb)

Cohort 2 (25 February 2021 and Later)

Patients in cohort 2 will be randomized in a 1:1 allocation ratio to co-administered REGN10933+REGN10987 combination therapy, IV single dose at 1200 mg (or body weight equivalent) or 2400 mg (or body weight equivalent). The REGN10933+REGN10987 treatment arms will be adjusted according to body weight as defined in Table 2.

In phase 3 cohort 2, randomization will be stratified by country.

Cohort 3

Patients in cohort 3 will be randomized in a 1:1 allocation ratio to co-administered REGN10933+REGN10987 combination therapy IV single dose (no placebo). Patients in cohort 3 who are ≥18 years of age will follow the REGN10933+REGN10987 dose levels described for cohort 1 (1200 mg and 2400 mg). Patients in cohort 3 who are <18 years of age will follow the adjusted REGN10933+REGN10987 dose levels described in Table 2.

In phase 3 cohort 3, randomization will not be stratified.

8.7. Blinding

A pharmacist or qualified personnel at the site, not otherwise associated with the conduct of the study, will reconstitute the drug for IV administration. The drug infusion solution must be provided in identical form for active and placebo treatments, so that they remain indistinguishable to both study personnel and patients.

Study patients, the principal investigators, and study site personnel (with the exception of the unblinded pharmacist at each site) will remain blinded to all randomization assignments throughout the study. The Regeneron medical/study director, study monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all patient randomization assignments in all phases of the study.

Selected individuals from the Sponsor not involved in the conduct of the study may have access to unblinded phase 1 or phase 2 data as needed for safety review or other data review (see Section 6.2.2). The team performing the interim data reviews will be separate from the ongoing study team. No study personnel involved in the day-to-day conduct of the study will have access to any unblinded data before the database is locked for this study.

Anti-drug antibody, drug concentration, and biomarker results will not be communicated to the sites, and the Sponsor's blinded operational team will not have access to results associated with patient identification until after the database is locked.

8.8. Emergency Unblinding

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event and when a treatment decision is contingent on knowing the patient's treatment assignment.

If unblinding is required:

- Only the investigator will make the decision to unblind the treatment assignment
- Only the affected patients will be unblinded
- Unblinding is performed using the IWRS, which will notify the Sponsor. The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If the study pharmacist(s)/designee is not available, the investigator for the site will unblind the patient.

- If the IWRS is unavailable, the investigator will ask the unblinded study pharmacist(s)/designee to perform manual unblinding. All manual unblinding procedure will be adequately documented, including the reason why the IWRS was not used.
- The investigator will notify Regeneron and/or designee as soon as possible after unblinding the patient

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency and when a treatment decision is contingent on knowing the patient's treatment assignment. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

8.9. Treatment Logistics and Accountability

8.9.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label unblinded investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

The unblinded pharmacist will prepare the unblinded investigational product and dispense it in a blinded manner to the blinded study staff for administration to the patient.

Study drug will be stored at the site at a temperature of 2ºC to 8ºC. Storage instructions will be provided in the pharmacy manual.

8.9.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed at the site with approval by the Sponsor or returned to the Sponsor or designee.

8.9.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication:

- Dispensed to each patient
- Returned from each patient (if applicable), and
- Disposed of at the site or returned to the Sponsor or designee.

All accountability records must be made available for inspection by the Sponsor and regulatory agency inspectors; photocopies must be provided to the Sponsor at the conclusion of the study.

8.9.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the Sponsor and regulatory agency inspectors.

8.10. Concomitant Medications

Any treatment or procedure administered from the first dose of study drug to the final study visit will be considered a concomitant medication or procedure. This includes medications and procedures that were started before the study and are ongoing during the study.

For more information on recording of concomitant medications and procedures, refer to Section 9.2.4.3.

8.10.1. Prohibited and Permitted Medications

Patients are not permitted to receive any medication specified in the exclusion criteria for study enrollment (Section 7.2.2) unless medically indicated. Patients may otherwise continue their normal regimen of medications and procedures.

Based on CDC guidance and investigator discretion, deferring the use of any authorized or approved COVID-19 vaccine for at least 90 days after dosing may be considered to reduce potential interference of the study drug with vaccine-induced immune responses. For more information, refer to the current CDC guidance (CDC, 2020a).

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 3 (phase 1), Table 4 (phase 2), Table 5 (phase 3 cohort 1; cohort 3 ≥18 years), and Table 6 (phase 3 cohort 2; cohort 3 <18 years).

Table 3: Schedule of Events: Phase 1

Day	Screening/Baseline Visit[1]				Mandatory / Optional Sequester[2]		Optional Sequester[2]				Follow Up								EOS
	-1 to 1				2	3	4	5	6	7	8[3]	9	11	13	15[3]	18	22[3]	25	29
	Screen	Pre-Dose	Dose	Post-Dose															
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Window (Days)												±1	±1	±1	±1	±1	±1	±1	±3
Screening/Baseline Only																			
Informed consent	X																		
[redacted]	X																		
Inclusion/exclusion	X																		
Molecular diagnostic test for SARS-CoV-2[5]	X																		
Demographics	X																		
Medical history (including COVID-19 illness)	X																		
Weight and height	X																		
Randomization		X																	
Treatment																			
Study drug administration			X																
Efficacy																			
Medically-attended COVID-19 visit details											X				X		X		X
Saliva sample for SARS-CoV-2 RT-qPCR		X				X		X		X		X	X	X	X	X	X	X	X
Nasal swab for SARS-CoV-2 RT-qPCR		X				X		X		X		X	X	X	X	X	X	X	X
NP swab for SARS-CoV-2 RT-qPCR		X				X		X		X		X	X	X	X	X	X	X	X
Safety																			
Vital signs		X[6]	X[6]	X[6]															
Treatment-emergent grade ≥2 IRRs[7]			← continuous monitoring →																
Treatment-emergent grade 3 or 4 AEs[7]			← continuous monitoring →																
Treatment-emergent SAEs[7]			← continuous monitoring →																
Treatment-emergent grade ≥2 hypersensitivity[7]			← continuous monitoring →																
Targeted concomitant medications[8]	X		X	X	X	X	X	X	X	X	X				X		X		X
Pregnancy test (WOCBP)[9]	X																		X
Central Laboratory Testing																			
Hematology (including differential)	X[10]									X									X

Day	Screening/Baseline Visit[1]				Mandatory / Optional Sequester[2]		Optional Sequester[2]				Follow Up								EOS
	-1 to 1																		
	Screen	Pre-Dose	Dose	Post-Dose	2	3	4	5	6	7	8[3]	9	11	13	15[3]	18	22[3]	25	29
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Window (Days)												±1	±1	±1	±1	±1	±1	±1	±3
Blood chemistry (including AST, ALT, CRP ferritin, LDH)	X[10]									X									X
Coagulation tests (D-dimer, PT/INR, aPTT)	X[10]									X									X
Central PK and Immunogenicity Testing																			
Serum for PK[11]		X[12]		X[12]		X		X		X					X				X
Serum for ADA[13]		X[13]																	X
Central Biomarker Testing																			
Serum for serology		X				X				X									X
Serum for cytokines		X				X				X									X
Plasma for complement		X				X				X									X
Serum for research		X				X				X									X
Plasma for research		X				X				X									X
Exploratory Patient-Reported Symptoms																			
SE-C19[14]		X		X	Daily														X
PGIS[14]		X		X	Daily														X
PGIC[14]																			X
[redacted]																			
[redacted]		[redacted]																	
[redacted]		[redacted]																	

ADA, anti-drug antibodies; AE; adverse event; ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; CRP, c-reactive protein; EOS, end of study; INR, international normalized ratio; IRR, infusion-related reaction; LDH, lactate dehydrogenase; NP, nasopharyngeal; PGIC, Patient Global Impression of Change of symptoms associated with COVID-19; PGIS, Patient Global Impression of Severity of symptoms associated with COVID-19; [redacted]; PK, pharmacokinetics; PT; prothrombin time; SAE, serious adverse event; RT-PCR, reverse transcription polymerase chain reaction; RT-qPCR, quantitative reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SE-C19, Symptom Evolution of COVID-19; WOCBP, women of childbearing potential.

Table 4: Schedule of Events: Phase 2 (and Phase 3 Prior to Protocol Amendment 6)

Note: For more information on patients in phase 3 who initially enrolled prior to phase 3 adaptations, refer to Section 6.1.3.

Day	Screening/Baseline Visit[1]				Follow Up													EOS
	-1 to 1																	
	Screen	Pre-Dose	Dose	Post-Dose	2	3	4	5	7	8[3]	9	11	13	15[3]	18	22[3]	25	29
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12	13	14	15
Window (Days)	X								±1	±1	±1	±1	±1	±1	±1	±1	±1	±3
Screening/Baseline Only																		
Informed consent	X																	
[redacted]	X																	
Inclusion/exclusion	X																	
Antigen or molecular diagnostic test for SARS-CoV-2[5]	X																	
Demographics	X																	
Medical history (including COVID-19 illness)	X																	
Weight and height	X																	
Randomization		X																
Treatment																		
Study drug administration			X															
Efficacy																		
Medically-attended COVID-19 visit details										X				X		X		X
NP swab for SARS-CoV-2 RT-qPCR		X				X		X	X		X	X	X	X	X	X	X	X
Safety																		
Vital signs		X[6]		X[6]														
Treatment-emergent grade ≥2 IRRs[7]			← continuous monitoring →															
Treatment-emergent SAEs[7]			← continuous monitoring →															
Treatment-emergent grade ≥2 hypersensitivity[7]			← continuous monitoring →															
Targeted concomitant medications[8]	X		← continuous monitoring →															
Pregnancy test (WOCBP)[9]	X																	X
Central Laboratory Testing																		
Hematology (including differential)	X[10]								X					X				X

Day	Screening/Baseline Visit[1]				Follow Up													EOS
	-1 to 1																	
	Screen	Pre-Dose	Dose	Post-Dose	2	3	4	5	7	8[3]	9	11	13	15[3]	18	22[3]	25	29
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12	13	14	15
Window (Days)	X								±1	±1	±1	±1	±1	±1	±1	±1	±1	±3
Blood chemistry (including AST, ALT, CRP ferritin, LDH)	X[10]								X					X				X
Coagulation tests (D-dimer, PT/INR, aPTT)	X[10]								X					X				X
Central PK and Immunogenicity Testing																		
Serum for PK[11]		X[12]		X[12]														X
Serum for ADA[13]		X[13]																X
Central Biomarker Testing																		
Serum for serology		X																X
Serum for cytokines and CK-MB		X							X					X				X
Serum for research and cardiac biomarkers		X							X					X				X
Plasma for research and cardiac biomarkers		X							X					X				X
Plasma for hsTroponin-T[14]		X							X					X				X
Exploratory Patient-reported Symptoms																		
SE-C19[14]		X			Daily													
PGIS[14]		X			Daily													
PGIC[14]																		X
[redacted]																		
[redacted]		[redacted]																
[redacted]		[redacted]																

ADA, anti-drug antibodies; AE; adverse event; ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; CK-MB, creatine kinase-MB, CRP, c-reactive protein; EOS, end of study; INR, international normalized ratio; IRR, infusion-related reaction; LDH, lactate dehydrogenase; NP, nasopharyngeal; PGIC, Patient Global Impression of Change of symptoms associated with COVID-19; PGIS, Patient Global Impression of Severity of symptoms associated with COVID-19; [redacted] PK, pharmacokinetics; PT, prothrombin time; PT, prothrombin time; SAE, serious adverse event; RT-PCR, reverse transcription polymerase chain reaction; RT-qPCR, quantitative reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SE-C19, Symptom Evolution of COVID-19; WOCBP, women of childbearing potential.

Table 5: Schedule of Events: Phase 3 (Cohort 1 Patients; Cohort 3 Patients ≥18 Years)

Day	Screening/Baseline Visit[1]				Follow Up[3]										EOS[3]
	-1 to 1				2	3	4	7	15	22	29	60	90	120	169
	Screen	Pre-Dose	Dose	Post-Dose											
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12
Window (Days)								±1	±3	±3	±3	±3	±3	±7[12]	±7
Screening/Baseline Only															
Informed consent	X														
[redacted]	X														
[redacted]	X														
Inclusion/exclusion	X														
Antigen or molecular diagnostic test for SARS-CoV-2[5]	X														
Demographics	X														
Medical history (including COVID-19 illness, risk factors)	X														
Weight and height	X														
Randomization (treatment assignment)		X													
Treatment															
Study drug administration			X												
Efficacy															
Query for COVID-19-related medically-attended visit details								X	X	X	X				
NP swab for SARS-CoV-2 RT-qPCR		X						X	X		X				
Safety															
Vital signs		X[6]		X[6]											
Treatment-emergent grade ≥2 IRRs[7,8]			X	X	← cont. mon. →										
TEAEs that led to ***any*** medically-attended visit[7,8]				X	← continuous monitoring →										
Treatment-emergent grade ≥2 hypersensitivity[7,8]			X	X	← continuous monitoring →										
Treatment-emergent SAEs[7,8,16]			X	X	← continuous monitoring →										
Targeted concomitant medications[7, 8]	X		X	X	← continuous monitoring →										
Concomitant procedures[7,8]	X		X	X	← continuous monitoring →										
Vital status[16]														X	X
Pregnancy test (women of childbearing potential)[9]	X														
Pregnancy status[16]														X	X
Safety information (newborns of study participants)[16]														X	X
Central Laboratory Safety Testing															
Hematology (including differential)	X[10]							X	X		X				

Day	Screening/Baseline Visit[1]				Follow Up[3]										EOS[3]
	-1 to 1				2	3	4	7	15	22	29	60	90	120	169
	Screen	Pre-Dose	Dose	Post-Dose											
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12
Window (Days)								±1	±3	±3	±3	±3	±3	±7[12]	±7
Blood chemistry (including AST, ALT, CRP, LDH)	X[10]							X	X		X				
Coagulation tests (D-dimer, PT/INR, aPTT)	X[10]							X	X		X				
Central Laboratory Immunogenicity Testing (Not Enrolled in PK Sub-Study, Not Pregnant at Randomization)															
Serum for ADA[13]	X[13]										X				
Central Laboratory Drug Concentration and Immunogenicity Testing (Enrolled in PK Sub-Study, Not Pregnant at Randomization)															
Serum for drug concentration (PK)[12]	X[10,12]										X[12]			X[12]	
Serum for ADA[13]	X[13]										X[13]			X[13]	
Central Laboratory Drug Concentration and Immunogenicity Testing (Pregnant at Randomization)															
Serum for drug concentration (PK)[12]	X[10,12]		X[12]								X[12]			X[12]	
Serum for ADA[13]	X[13]										X[13]			X[13]	
Central Laboratory Biomarker Testing															
Serum for serology	X[10]										X				
Serum for research	X[10]							X	X		X				
Plasma for research	X[10]							X	X		X				
Exploratory Patient-reported Outcomes															
SE-C19[14]		X			Daily										
PGIS[14]		X			Daily										
PGIC[14]											X				
Item: return to usual health[14]		X			Daily										
Item: return to usual activities[14]		X			Daily										
EQ-5D-5L[14]		X			Daily							X[14]	X[14]	X[14]	X[14]
WPAI+CIQ[14]								X	X	X	X				
[redacted]															
[redacted]		X									X				
[redacted]															
[redacted]															
[redacted]															

ADA, anti-drug antibodies; AE; adverse event; ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; CRP, c-reactive protein; EOS, end of study; INR, international normalized ratio; IRR, infusion-related reaction; LDH, lactate dehydrogenase; NP, nasopharyngeal; PBMC, peripheral blood mononuclear cells; [redacted]; PK, pharmacokinetics; PT, prothrombin time; SAE, serious adverse event; RT-qPCR, quantitative reverse transcription polymerase chain reaction; TEAE, treatment-emergent adverse event.

Table 6: Schedule of Events: Phase 3 (Cohort 2 Patients; Cohort 3 Patients <18 Years)

Day	Screening/Baseline Visit[1]				Follow Up[3]										EOS[3]
	-1 to 1				2	3	4	7	15	22	29	60	90	120	169
	Screen	Pre-Dose	Dose	Post-Dose											
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12
Window (Days)								±1	±3	±3	±3	±3	±3	±7	±7
Screening/Baseline Only															
Parental informed consent and informed assent	X														
Inclusion/exclusion	X														
Antigen or molecular diagnostic test for SARS-CoV-2[5]	X														
Demographics	X														
Medical history (including COVID-19 illness, risk factors)	X														
Weight and height	X														
Randomization (treatment assignment)		X													
Randomization (PK-ADA schedule assignment)[15]		X													
Treatment															
Study drug administration			X												
Efficacy															
Query for COVID-19-related medically-attended visit details		X						X	X	X	X				
NP swab for SARS-CoV-2 RT-qPCR		X				X		X	X		X				
Safety															
Vital signs (≥12 years)		X[6]		X[6]											
Vital signs (<12 years)		X[6]	X[6]	X[6]											
Treatment-emergent grade ≥2 IRRs[7, 8]			X	X[17]	← cont. mon. →										
TEAEs that led to ***any*** medically-attended visit[7, 8]				X[17]	← continuous monitoring →										
Treatment-emergent grade ≥2 hypersensitivity[7, 8]			X	X[17]	← continuous monitoring →										
Treatment-emergent grade 3 or 4 AEs[8]			X	X[17]	← continuous monitoring →										
Treatment-emergent SAEs[7, 8,16]			X	X[17]	← continuous monitoring →										
Targeted concomitant medications[7,8]	X		X	X[17]	← continuous monitoring →										
Concomitant procedures[7,8]	X		X	X[17]	← continuous monitoring →										
Vital status[16]														X	X
Pregnancy test (women of childbearing potential)[9]	X														
Pregnancy status[16]														X	X
Safety information (newborns of study participants)[16]														X	X

Day	Screening/Baseline Visit[1]				Follow Up[3]										EOS[3]
	-1 to 1				2	3	4	7	15	22	29	60	90	120	169
	Screen	Pre-Dose	Dose	Post-Dose											
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12
Window (Days)								±1	±3	±3	±3	±3	±3	±7	±7
Central Laboratory Safety Testing and Central Laboratory Biomarker Testing, Body Weight ≥20 kg															
Hematology (including differential)	X[10]							X	X		X				
Blood chemistry (including AST, ALT, CRP, LDH)	X[10]							X	X		X				
Serum for serology	X[10]										X				
Serum for exploratory research	X[10]							X	X		X				
Plasma for exploratory research	X[10]							X	X		X				
Central Laboratory Safety Testing and Central Laboratory Biomarker Testing, Body Weight ≥10 kg to <20 kg															
Hematology (including differential)	X[10]							X	X		X				
Blood chemistry (including AST, ALT, CRP, LDH)	X[10]							X	X		X				
Serum for serology	X[10]										X				
Central Laboratory Safety Testing and Central Laboratory Biomarker Testing, Body Weight <10 kg															
Hematology (including differential)	X[10]							X			X				
Blood chemistry (including AST, ALT, CRP, LDH)	X[10]							X			X				
Serum for serology	X[10]														
Central Laboratory Drug Concentration and Immunogenicity Testing (All Body Weight Tiers)															
Serum for PK-ADA (Schedule A)[15]	X[10,12]			X[12]		X[12]					X[12]				
Serum for PK-ADA (Schedule B)[15]	X[10,12]			X[12]				X[12]			X[12]				
Serum for PK-ADA (Schedule C)[15]	X[10,12]			X[12]					X[12]		X[12]				
Serum for PK-ADA (Schedule D)[15]	X[10,12]			X[12]						X[12]	X[12]				
Exploratory Patient-reported Outcomes (Age ≥12 Years Only)[14]															
SE-C19[14]		X			Daily										
PGIS[14]		X			Daily										
PGIC[14]											X				
Item: return to usual health[14]		X			Daily										
Item: return to usual activities[14]		X			Daily										
EQ-5D-Y[14]		X			Daily							X[14]	X[14]	X[14]	X[14]
WPAI+CIQ[14]								X	X	X	X				

ADA, anti-drug antibodies; AE; adverse event; ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; CRP, c-reactive protein; EOS, end of study; INR, international normalized ratio; IRR, infusion-related reaction; LDH, lactate dehydrogenase; NP, nasopharyngeal; [redacted]; PK, pharmacokinetics; PT, prothrombin time; SAE, serious adverse event; RT-qPCR, quantitative reverse transcription polymerase chain reaction; TEAE, treatment-emergent adverse event.

9.1.1. Footnotes for the Schedule of Events Tables

1. Screening visit may occur on the same day as, or the day prior to, the baseline visit.
2. [Phase 1 footnote removed]
3. On visit days where in-person sample collections or assessments are not required, information may be collected by phone.

[redacted]

5. Refer to Section 9.2.1.2 for diagnostic test requirements during screening.
6. Vital signs, including temperature, blood pressure, heart rate, and SpO_2 will be collected as described in Section 9.2.4.1.

   For **patients in cohort 1 and patients ≥12 years in cohort 2 and cohort 3**, vital signs will be taken once before the infusion and once after the infusion is completed. After infusion of study drug, these patients will be observed for at least 1 hour.

   For patients in **patients <12 years in cohort 2 and cohort 3**, vital signs will be taken before infusion, approximately every 30 minutes during the infusion, after the infusion is completed, approximately 1-hour post-infusion, and approximately 2 hours post-infusion. After infusion of study drug, these patients will be observed for at least 2 hours.
7. Treatment-emergent AESIs (grade ≥2 IRRs, grade ≥2 hypersensitivity, and TEAEs associated with ***any*** medically-attended visit) and treatment-emergent SAEs will be recorded until day 29. From day 30 to day 169, only treatment-emergent SAEs will be recorded. **For patients in cohort 2 and patients <18 years in cohort 3**, treatment-emergent grade 3 or 4 AEs will also be recorded until day 29. Refer to Section 10 for more information on reporting and recording requirements.

   Targeted concomitant medications and concomitant procedures will also be reviewed and recorded. Refer to Section 9.2.4.3 for more information.
8. Continuously-monitored events will be recorded when they occur during the corresponding time period marked on the schedule of events. Study visits (including phone calls) are not required solely to collect continuously-monitored assessments, if no other assessments are planned on that day.
9. Pregnancy testing will be performed in women of childbearing potential (WOCBP) only and regardless of pregnancy status. A negative test is **not required** prior to study drug

administration. Serum or urine pregnancy test are both acceptable. Refer to Section 9.2.6 for more information, including a definition of WOCBP.

Note that a paper pregnancy report form must be completed for each patient who becomes pregnant or is pregnant at the signing of consent.

10. The indicated blood samples may be collected at the either day -1 or day 1 (ie, screening or pre-dose), but must be collected prior to randomization. For patients in phase 3 cohort 2, efforts should be made to collect all screening/pre-dose blood samples on the same study visit, when feasible.
11. [Footnote removed]
12. Actual dosing time and drug concentration sample collection times, as applicable, will be recorded.

    At the screening/baseline visit, blood for assessment of drug concentration in serum will be taken prior to dosing and within 60 minutes after the end of infusion (EOI). The EOI sample should be collected from the arm contralateral to that used for IV infusion. If not medically feasible, the EOI sample can be drawn from the same arm, but not from the infusion catheter.

    In cohort 1 and cohort 3 (≥18 years old), patients will follow different blood sample collection schedules for drug concentration and immunogenicity depending on whether they enrolled in the PK sub-study (cohort 1), not enrolled in the PK sub-study (cohort 1), or are pregnant at randomization (cohort 3 patients ≥18 years old). For samples collected on day 120, the collection window is ±28 days. Refer to Section 9.2.8 for more information on the PK sub-study.
13. The window for predose ADA sample collection is as close to administration of study drug as is reasonable. Actual dosing time and ADA sample collection times, as applicable, will be recorded.
14. **Patients in cohort 1 and patients ≥12 years in cohort 2 and cohort 3** will self-report symptoms using electronic surveys. The order of completion is as follows: SE-C19, PGIS, PGIC, return to usual health, return to usual activities, EQ-5D-5L (or EQ-5D-Y), WPAI+CIQ. On days when a survey/questionnaire is not required it will be skipped, but the overall order will remain the same. Note that the return to usual health, return to usual activities, WPAI+CIQ, EQ-5D-5L, and EQ-5D-Y will only be administered at sites when regionally available.

    On days 60 and 90 the window for EQ-5D-5L (or EQ-5D-Y) assessment is ±3 days. On days 120 and 169, the window is ±7 days. Note that study visits are not required on days when only electronic survey data are collected.

15. In **cohort 2 (and patients <18 years in cohort 3)**, each patient will be assigned at randomization by IWRS to a blood sample collection schedule for drug concentration and immunogenicity analysis. Actual dosing time and PK-ADA sample collection times will be recorded. To conserve blood volume, a single blood draw for drug concentration and immunogenicity will be obtained.
16. Patients will be followed by phone at day 120 and day 169 for vital status, pregnancy status, targeted safety information, and additional safety information in newborns of study participants. Refer to Section 9.2.5 for more information on these follow-up assessments.
17. **For patients <12 years in cohort 2 and cohort 3**, follow-up by phone will be conducted within 6 to 8 hours of infusion to collect the information indicated.

9.1.2. Early Termination from the Study

Patients who are withdrawn from the study will be asked to allow an early termination visit consisting of day 29 assessments and sample collections.

9.1.3. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of treatment-emergent SAEs, treatment-emergent AESIs, or for any other reason, as warranted.

9.2. Study Procedures

This section describes the procedures and collections that will be performed in this study. Procedures and collections will occur according to the schedule of events (Section 9.1).

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population.

9.2.1.1. Informed Consent

Informed consent (and assent, as applicable) must be obtained according to the requirements described in Section 13.2. [redacted]

9.2.1.2. Diagnostic Test for SARS-CoV-2

The investigator or sub-investigator will verify that the patient has tested positive for SARS-CoV-2, either at screening or by historical record (refer to Section 7.2.1 for detailed screening requirements). For tests performed at screening, the local testing result, specimen type, assay type, and date of the test will be recorded in the eCRF.

9.2.1.3. Demographics

Refer to Section 5.1.

9.2.1.4. Medical History

Medical history will include the following:

- COVID-19 with start date as the date of onset of first symptoms related to COVID-19
- Risk factors for severe COVID-19/hospitalization due to COVID-19, as defined in Section 7.2.1
- Whether the patient is receiving oxygen at home by nasal cannula
- Menopausal history
- Pregnancy or breastfeeding status, if applicable

9.2.1.5. Weight and Height

Weight and height will be recorded at the screening/baseline visit.

9.2.2. Treatment

See Section 8.1.

9.2.3. Efficacy Procedures

9.2.3.1. Nasopharyngeal Swab Collection

Nasopharyngeal (NP) swab samples will be collected from patients to determine presence or absence of SARS-CoV-2 virus, including at baseline, and to measure viral load. Samples will be used for RT-qPCR analysis. Samples collected from patients may additionally be used for exploratory viral RNA sequencing, plaque forming unit assays (PFU) assays and/or viral culture. Additional details regarding sample collection and analysis can be found in Section 9.2.10.3 and the laboratory manual.

9.2.3.2. COVID-19-Related Medically-Attended Visit Details

A COVID-19-related medically-attended visit will be defined as follows: hospitalization, emergency room (ER) visit, urgent care visit, physician's office visit, or telemedicine visit, with the primary reason for the visit being COVID-19.

Medically-attended visits related to COVID-19, as determined by the investigator, will be recorded in the eCRF. During each indicated collection visit (refer to Table 5 and Table 6 for collection visits in phase 3), all previously unrecorded COVID-19-related medically-attended visits and details will be recorded, beginning from the day of dosing up to and including the day of collection.

Details will include at minimum:

- Type of visit (hospitalization, ER, urgent care, physician's office visit, telemedicine)
- Date of visit
- If hospitalized due to COVID-19, length of visit

- Reason (list all COVID-19-related symptom[s] or clinical manifestation[s]) that prompted medically-attended visit)
- If hospitalized due to COVID-19, whether ICU care was given
- If hospitalized due to COVID-19, whether mechanical ventilation was required
- Treatments given for COVID-19 (including, but not limited to supplemental oxygen, corticosteroids, COVID-19 convalescent plasma, remdesivir, bamlanivimab, etc)

9.2.4. Safety Procedures

9.2.4.1. Vital Signs

Vital signs will include temperature, blood pressure, heart rate (per minute), SpO_2. For phase 1, respiratory rate (per minute) will also be assessed.

Temperature may be measured using the following methods: axilla, oral, tympanic, or temporal. Body temperature should be measured using the same method each time. Temperature should be measured after at least 5 minutes of rest (supine or sitting).

Blood pressure should be measured after the patient has been resting quietly for at least 5 minutes and may be obtained from a seated or supine position.

SpO_2 will be measured using a fingertip or similar non-invasive device following 5 minutes of rest (inactivity) while supine, semi-recumbent, or sitting and will only be measured in the presence of a good SpO_2 wave form.

9.2.4.2. Adverse Event Monitoring

Targeted TEAEs (as defined in Section 10.1.1) will be recorded.

Note that any symptoms collected by SE-C19, PGIC, or PGIS (Section 9.2.10.8) may not necessarily be considered adverse events.

9.2.4.3. Record Targeted Concomitant Medications and Concomitant Procedures

A targeted list of the following concomitant medications will be recorded in the eCRF:

- Putative COVID-19 treatments (eg, remdesivir, bamlanivimab, convalescent serum, IVIG, IL-6 receptor inhibitors [eg, sarilumab, tocilizumab], JAK inhibitors [eg, baricitinib], ivermectin)
- Oxygen
- SARS-CoV-2 vaccinations
- Influenza vaccinations
- Any other vaccinations
- Antipyretics (eg, aspirin, acetaminophen, ibuprofen)
- Anticoagulants (eg, enoxaparin, warfarin, rivaroxaban)
- Immunosuppressants (eg, cyclosporine A, corticosteroids)

- Interferon beta
- Theophylline
- Antiepileptics (eg, carbamazepine, divalproex, phenytoin)
- Antiarrhythmics (eg, digoxin, disopyramide, procainamide)
- Antivirals, antibacterials, and antifungals
- Antiparasitics (chloroquine or hydroxychloroquine)
- Angiotensin receptor blockers (eg, losartan, valsartan)
- Angiotensin converting enzyme inhibitors (eg, benazepril, lisinopril)
- Any medication used to treat an adverse event

In addition, any concomitant procedures used to treat an adverse event will be recorded in the eCRF.

For more information on concomitant medications and procedures, refer to Section 8.10.

9.2.5. Post-Day 29 Follow-up by Phone

In phase 3, patients (and/or their parent or legal guardian) will be contacted by phone for post-day 29 safety assessments at the time points listed in the respective schedules of events. These assessments will include vital status, pregnancy status, and targeted safety information.

Vital Status. Record vital status (whether the patient is dead or alive) and record the date of death, when applicable.

Pregnancy Status. Record pregnancy status and date of pregnancy, when applicable. Refer to Section 10.1.3 for reporting requirements.

Targeted Safety Information. Refer to Section 10 for more information on reporting and recording requirements.

Safety Information in Newborns of Study Participants. The incidence and outcome of any SARS-CoV-2 infection will be collected for newborn infants of patients who were treated in the study and were pregnant at randomization or became pregnant at any time in the study. Note that this information is in addition to outcome reporting of all pregnancies (Section 10.1.3).

9.2.6. Pregnancy Test for Women of Childbearing Potential

Pregnancy testing may be satisfied by either serum pregnancy test or by urine β-HCG. Pregnancy tests are a requirement for WOCBP only and should be completed regardless of pregnancy status. Pregnancy test will be performed at the local laboratory.

WOCBP are defined as females who are fertile following menarche until becoming postmenopausal, unless permanently sterile. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a

postmenopausal state. The above definitions are according to Clinical Trial Facilitation Group (CTFG) guidance. Pregnancy testing is not required for women with documented hysterectomy or tubal ligation.

Information about pregnancy will be recorded as described in Section 10.1.3.

9.2.7. Laboratory Testing

Hematology and blood chemistry will be analyzed by a central laboratory. Detailed instructions are provided in the laboratory manual.

Blood Chemistry

Tests will include:

Sodium	Blood urea nitrogen (BUN)	Alkaline phosphatase
Potassium	Aspartate aminotransferase (AST)	Creatinine
Chloride	Alanine aminotransferase (ALT)	Creatine phosphokinase (CPK)
Carbon dioxide	Total bilirubin	Lactate dehydrogenase (LDH)
Glucose	Albumin	C-reactive protein

Hematology

Tests will include:

Hemoglobin	*Differential:*	Neutrophils
Hematocrit		Lymphocytes
Red blood cells (RBCs)		Monocytes
White blood cells (WBCs)		Basophils
Platelet count		Eosinophils

Other Laboratory Tests

Coagulation tests: D-dimer, prothrombin time (PT/INR), activated partial thromboplastin time (aPTT).

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the Medical/Study Director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values are provided in Section 10.1.1.

9.2.8. Drug Concentration Measurements and Samples

Samples for assessment of drug concentration will be collected at the timepoints indicated in the schedule of events. For information concerning unused samples and exploratory research, refer to Section 9.2.10.

In phase 3 cohort 1, approximately 600 patients will be enrolled in a PK sub-study (refer to Table 5). This sub-study will only be enrolled at a select number of participating sites. In cohort 1, only patients who are enrolled in the PK sub-study will have samples collected for drug concentrations. Additional samples for immunogenicity assessment will be also collected in these patients.

9.2.9. Immunogenicity Measurements and Samples

Samples for immunogenicity assessment will be collected for adult patients at the timepoints listed in the relevant schedule of events. For pediatric patients, samples will be collected as described in the Table 6 and may be assessed for ADA and NAb, if feasible. For information concerning unused samples and exploratory research, refer to Section 9.2.10.

9.2.10. Exploratory Pharmacodynamic/Biomarker Analyses

This section describes planned exploratory pharmacodynamic/biomarker analyses, some of which may not be reported in the CSR. Note that, in this adaptive master protocol, the analyses described in this section may be limited to particular or study phases or time periods during a study phase.

Also note that any biological samples collected during the study which are not used for their planned purpose, or for which material remains after their planned analysis, may be kept for up 15 years after study completion (or for a shorter time period if required per regional laws and regulations) for use in exploratory research related to how the study drugs work and to study SARS-CoV-2.

9.2.10.1. Neutrophil–Lymphocyte Ratio

Exploratory biomarkers, including the neutrophil-lymphocyte ratio (NLR), will be assessed. Neutrophil-lymphocyte ratio is as an inflammatory biomarker and is suggested to be an independent risk factor of the in-hospital mortality for COVID-19 patients. Assessment of NLR trends may help identify individuals with COVID-19 at higher risk of complications (Liu, 2020) (Qin, 2020). We will measure NLR as an exploratory endpoint and, as compared to placebo, and association with clinical endpoints will be evaluated.

9.2.10.2. Serum and Plasma Biomarkers

Changes in circulating concentrations of serum/plasma biomarkers associated with inflammation, coagulation, and disease progression will be assessed in REGN10933+REGN10987 group compared to the placebo group in phase 1 and phase 2. The association between changes in disease related biomarkers with clinical endpoints may be evaluated.

Biomarkers may include (but are not limited to) CRP, LDH, D-dimer, and ferritin. CRP is a general inflammation marker that correlates with severity of COVID-19 including lung lesions, supplemental O_2 requirements, and death (Luo, 2020) (Qin, 2020). LDH was identified as a predictive factor for early recognition of lung injury and advanced COVID-19 cases (Ruan, 2020)

(Wang, 2020b) (Young, 2020). Ferritin is a general inflammation marker associated with severity of COVID-19 (Qin, 2020). D-dimer levels >1 µg/mL have been reported to identify patients with poor prognosis for COVID-19 (Zhou, 2020).

9.2.10.3. Virology

Viral Sequencing

In support of public health initiatives to track SARS-CoV-2 genetic variants, as well as to monitor for possible viral resistance, viral genome sequencing may be performed on viral nucleic acid isolated from nasopharyngeal swab, nasal swab, and/or saliva samples, at baseline and in cases of a positive RT-qPCR result. Sequencing analyses will consist of the entire viral genome, including the full gene sequence that encodes the SARS-CoV-2 S protein.

Viral sequencing may be performed on post-treatment samples to assess the emergence of sequence variants and to understand the potential relationship between genetic mutations and mAb functional activity. Viral sequencing may also be done on placebo controls to determine whether any genetic mutations observed in the mAb treatment group are naturally emergent genetic variants.

Viral variants suspected to confer decreased susceptibility to REGN10933 and/or REGN10987 will be evaluated in nonclinical work separate from this protocol.

The results of viral sequencing will be reported separately from the CSR.

Viral Infectivity

To explore the effects of REGN10933+REGN10987 on infectivity of SARS-CoV-2, we may use PFU, viral culture or viral subgenomic mRNA RT-qPCR assays. In vitro SARS-CoV-2 infectivity of cultured cells may be explored using NP samples. Infectivity of cells grown in culture may be assessed by PFU assays and/or immunofluorescence assays. We may also use sub-genomic viral mRNA transcript assays, such as RT-qPCR or subgenomic mRNA sequencing, or other measures of in vivo infectivity potential. Viral sub-genomic mRNA is transcribed only in infected cells and is not packaged into virions, and therefore may be an indicator of actively-infected cells. These data may be associated with RT-qPCR measuring viral load.

The results of the viral infectivity assays may not be included in the clinical study report.

9.2.10.4. Serological Immunoassays for Anti-SARS-CoV-2 Antibodies

To explore the impact of baseline humoral activity against SARS-CoV-2 on the response to REGN10933+REGN10987, serological immunoassays will be used to detect antibodies at baseline against the SARS-CoV-2 S protein and/or N protein. Neutralization assays may also be used to evaluate the function of endogenous baseline anti-SARS-CoV-2 antibodies. Associations will be evaluated with clinical outcomes. Measurement of antibodies against the N protein post-treatment will also be used to evaluate whether or not REGN10933+REGN10987 effect the endogenous humoral immune response to SARS-CoV-2.

9.2.10.5. Serum and Plasma for Exploratory Research

Research serum and plasma are being collected and banked for exploratory research related to COVID-19, SARS-CoV-2, REGN10933+REGN10987, host and viral biological pathways, and

other mechanisms related to disease activity and clinical outcomes. These serum and plasma samples may be used for complement and/or cytokine analysis (described below), as well as other analyses.

9.2.10.6. Complement

Complement activation has been hypothesized to contribute to the maladaptive inflammatory response seen in some patients with advanced COVID-19. Circulating complement biomarker concentrations may therefore be assessed in order to understand the involvement of the classical lectin and/or alternative complement pathways in the pathogenesis of COVID-19 and clinical outcomes.

9.2.10.7. Cytokines

The initial inflammatory responses to an infection are rapid and non-specific, regulated by proinflammatory cytokines such as interleukin-6 (IL-6). As IL-6 has been implicated in the severity of COVID-19, IL-6 and other cytokines, including but not limited to IL-8, IL-1ß, IFNγ, TNFα, IL-10 and MIP-1β may be measured. Additional cytokines may be interrogated through the use of cytokine panels.

9.2.10.8. Serum and Plasma for Cardiac Biomarkers

SARS-CoV-2 has been shown to infect the myocardium, and emerging evidence suggests that myocardial damage may be a long-term clinical consequence of COVID-19 (Lindner, 2020) (Puntmann, 2020). Cardiac biomarkers, including troponins, N-terminal pro B-type natriuretic peptide (NT-proBNP), and creatine kinase-MB (CK-MB), can be elevated in patients with COVID-19 and have been shown to correlate with adverse outcomes (Puntmann, 2020) (Sandoval, 2020) (Shi, 2020). Relationships may be evaluated between these biomarkers, as well as other biomarkers and clinical outcomes in treatment versus placebo arms.

If initial analyses reveal no signal of cardiac injury, subsequent analyses may be omitted.

[redacted]

[redacted]

9.2.13. Exploratory Patient-Reported Symptoms

This section describes planned patient-reported symptom analyses, some of which may not be reported in the CSR. Note that, in this adaptive master protocol, the analyses described in this section may be limited to particular or study phases or time periods during a study phase. Note that any symptoms collected by the instruments described below will not be considered AEs and will not be reconciled with any AEs.

SE-C19, PGIS, and PGIC

The Symptom Evolution of COVID-19 (SE-C19) instrument was developed de novo by Regeneron with the aim to better understand the symptomatic course of COVID-19 infection over time and is based on current available evidence on symptoms of COVID-19 (Arentz, 2020) (Chen, 2020a) (Chen, 2020b) (Huang, 2020) (Lapostolle, 2020) (Mizrahi, 2020) (Song, 2020) (Wang, 2020a). Patients self-report symptoms using a compatible electronic device (eg, smartphone, tablet, laptop or personal computer). Patients are presented with a list of symptoms and are asked to identify all those that they are experiencing.

Patients rate each identified symptom as mild, moderate, or severe at the worst moment within the last 24 hours. An 'other' category is also available, where a free text field allows the addition of any symptom that is not on the list. Each score is assigned a numeric value: 0 (no symptom), 1 (mild symptom), 2 (moderate symptom), or 3 (severe symptom). Table 7 provides the symptoms evaluated in the SE-C19.

Table 7: Symptoms Evaluated in the SE-C19

SE-C19 Symptoms Recorded and Planned for Analysis		
• Body aches such as muscle pain or joint pain	• Chest pain	• Chills
• Confusion[1]	• Cough	• Diarrhea
• Dizziness	• Fatigue	• Feverish
• Headache	• Loss of appetite	• Loss of taste / smell
• Nausea	• Pressure / tight chest	• Rash[1]
• Red or watery eyes	• Runny nose	• Shortness of breath / difficulty breathing
• Sneezing[1]	• Sore throat	• Sputum / phlegm
• Stomachache	• Vomiting[1]	

[1] Not included in the phase 3 key secondary analysis (Section 11.4.3.2)

To aid interpretation, the SE-C19 is supplemented by the Patient Global Impression of Change (PGIC) and the Patient Global Impression of Severity (PGIS), which assess the overall subjective experience of symptom severity and change in symptoms over time.

As a representation of the current available evidence of COVID-19 symptoms, the SE-C19 appears to have face validity for tracking symptom onset, severity, and recovery. Content validity was confirmed through an interview-based study of patients and clinicians, separate from this study.

WPAI+CIQ

Acute respiratory illnesses can lead to a significant economic burden owing to absenteeism and loss of workplace productivity (Li, 2007). The Work Productivity and Activity Impairment and Classroom Impairment Questions (WPAI+CIQ) questionnaire measures the effect of a specific health problem (eg, infection with SARS-CoV-2) on work productivity and activity impairment. The specific outcomes measured by the questionnaire are absenteeism (work time missed), presenteeism (impairment while working), overall work impairment (absenteeism plus presenteeism), and activity impairment (impairment in regular activities). Each score is represented as a percentage, with higher scores indicating less productivity or greater impairment.

EQ-5D-5L

The COVID-19 pandemic has resulted in a multisectoral global economic burden (Nicola, 2020), a significant portion of which is likely attributable to indirect costs related to school absenteeism, loss of workspace productivity, as well as health-related quality of life. Assessing the quality of life of individuals with SARS-CoV-2 is important, as it can aid in understanding the potential impact of interventions from the perspective of cost-utility analysis.

The EQ-5D-5L is a validated and extensively published self-reported quality of life scale. The EQ-5D-5L covers 5 health domains: mobility, self-care, usual activities, pain, and anxiety. Patients rate each domain on 5 level severity scale: having no problems, having slight problems, having moderate problems, having severe problems, and being unable to do/having extreme problems. In addition to the 5 domains, patients record their overall health on a visual analog scale, ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

The EQ-5D-Y is a youth version of the adult scale designed and validated for use by children. It includes also 5 domains: mobility, looking after myself, doing usual activities, having pain or discomfort and feeling worried, sad or unhappy.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

Only **targeted TEAEs** will be recorded:

- **All phases:** Treatment-emergent SAEs, up to day 29
- **Phase 1 and phase 2 only:** Treatment-emergent AESIs, defined as grade ≥2 IRRs and grade ≥2 hypersensitivity reactions (see Section 10.1.3), up to day 29
- **Phase 1 only:** TEAEs (grade 3 or grade 4 only), up to day 29
- **Phase 3 only, all cohorts:** Treatment-emergent AESIs, defined as grade ≥2 IRRs, grade ≥2 hypersensitivity reactions, **and** any TEAE that led to a medically-attended visit (see Section 10.1.3), up to day 29
- **Phase 3 only, all cohorts:** Treatment-emergent SAEs from day 30 to day 169
- **Phase 3 only, cohort 2 (and cohort 3 patients <18 years) only:** Grade 3 and grade 4 TEAEs, up to day 29

The investigator must promptly the above targeted TEAEs occurring during the observation period (see Section 11.4.5.1). Note that the length of this period differs in each study phase, owing to different final study visit days. Medical conditions that existed or were diagnosed prior to the signing of the informed consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of informed consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as TEAE, provided that it fulfills the above criteria.

Throughout the study, the investigator will determine whether any targeted TEAEs occurred by evaluating the patient. These events may be directly observed, reported spontaneously by the patient, or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all TEAEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The investigator's assessment must be clearly documented in the site's source documentation with the investigator's signature. The investigator should follow up on targeted TEAEs until they have resolved or are considered clinically stable.

Always report the diagnosis as the AE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, require corrective treatment, or constitute an AE in the investigator's clinical judgement. For events that are serious due to hospitalization, the reason for hospitalization

must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the informed consent form [ICF]) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE occurring subsequent to the reporting period (end of study) that the investigator assesses as related to study drug should be reported. In addition, any SAE resulting in death that occurs prior to study day 169 should also be reported, regardless of patient withdrawal or early termination.

All treatment-emergent SAEs, AESIs, and pregnancies are to be reported according to the procedures in Section 10.1.3.

10.1.2. Reporting Procedure

The targeted treatment-emergent AEs defined in Section 10.1.1 must be reported with investigator's assessment of the event's seriousness, severity, and causality to the blinded study drug. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE eCRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc) will be summarized in the narrative on the AE eCRF and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.1.3. Events that Require Expedited Reporting to Sponsor

The following events also require reporting to the Sponsor (or designee) within 24 hours of learning of the event:

Treatment-emergent SAEs.

Treatment-emergent AESI (serious and nonserious), defined as**:**

- Grade ≥2 infusion-related reactions
- Grade ≥2 hypersensitivity reactions
- **Phase 3 only:** Any treatment-emergent adverse event that led to a medically-attended visit, regardless of whether the visit is related to COVID-19

  Note: pre-planned or prescheduled medical appointments will not be considered medically-attended visits

- **Pregnancy.** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the Sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female study patient during the study or existing at the time of signing the informed consent form. A paper pregnancy report form must be completed for each patient who becomes pregnant or is pregnant at the signing of consent.

  Any complication of pregnancy affecting a female study patient and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the Sponsor, including testing results for SARS-CoV-2 infection in the newborn, if performed.

10.2. Definitions

10.2.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

10.2.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an adverse event that had occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** (admission after discharge) or **prolongation of existing hospitalization**. In-patient hospitalization is defined as a hospital admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event or is prolonged due to the development of a new adverse event as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** – Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood

dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events (refer to Section 10.1.1 Section 10.1.2).

10.2.3. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical interest specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

Adverse events of special interest for this study are defined in Section 10.1.3.

10.2.4. Infusion-Related Reactions and Hypersensitivity Reactions

Infusion-related reactions are defined as any relevant adverse events that occurs during the infusion or up to day 4.

Hypersensitivity reactions are defined as any relevant adverse event that occurs during the infusion or up to study day 29.

10.2.5. Severity

The severity of adverse events (including test findings classified as adverse events) will be graded using the current version of the NCI-CTCAE v5.0 (Division of Cancer Treatment and Diagnosis [DCTD], 2020).

Treatment-emergent AEs, SAEs or AESIs not listed in the NCI-CTCAE will be graded according to the scale in Table 8.

Table 8: NCI-CTCAE Severity Grading System for Adverse Events (v5.0)

Grade	Severity	Description
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate	Minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)[1]
3	Severe	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2]
4	Life-threatening	Life threatening consequences; urgent intervention indicated
5	Death	Death related to adverse events

[1] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[2] Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

10.2.6. Causality

The investigator must provide causality assessment as whether or not there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset versus time drug was administered
- Nature of the reactions: immediate versus long term
- Clinical and pathological features of the events
- Existing information about the drug & same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Patient's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The adverse event follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The adverse event follows a reasonable temporal sequence from study drug administration and is a known reaction to the drug under study or its class of drugs or is predicted by known pharmacology.
- Not Related:
  - The adverse event does not follow a reasonable sequence from study drug administration or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol specified procedure):

- Related:
  - The adverse event follows a reasonable temporal sequence from a protocol specified procedure and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:

– The adverse event does not follow a reasonable sequence from a protocol specified procedure or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

10.3. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the Sponsor in a timely fashion. The Sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Global Patient Safety; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

10.4. Notifying Health Authorities, Institutional Review Board, Ethics Committee, and Investigators

During the study, the Sponsor and/or the CRO will inform health authorities, ECs/Institutional Review Board (IRBs), and the participating investigators of any SUSARs (Suspected Unexpected Serious Adverse Reactions) occurring in other study centers or other studies of the active study drug, as appropriate per local reporting requirements. In addition, the Sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

Upon receipt of the Sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the IRB/EC unless delegated to the Sponsor.

Event expectedness for study drug is assessed against the Reference Safety Information section of the Investigator's Brochure that is effective for expedited safety reporting.

At the completion of the study, the Sponsor will report all safety observations made during the conduct of the trial in the Clinical Study Report to health authorities and ECs/IRB as appropriate.

11. STATISTICAL PLAN

This section provides the basis for the statistical analysis plans (SAPs) for the study. The SAPs may be revised during the study to accommodate amendments to the clinical study protocol, and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The initial phase 1/2 SAP describes the interim descriptive analysis of data from the first 275 symptomatic patients enrolled in this study. The phase 2 SAP describes the primary phase 2 analysis based on data from the first 799 symptomatic patients in the study. A SAP for phase 3 will provide additional details for the analysis of phase 3 data. The final SAPs will be issued before the database lock in each portion of the study.

This master protocol is intended to allow for adaptations, including dropping of a treatment group, addition of new treatment arms with other anti-SARS-CoV-2 S protein mAbs as they become available for clinical testing, determination of the primary endpoints for phase 3, and sample size

re-estimation for phase 2 and 3. Therefore, treatment groups in phase 3 and analyses for phase 3 will depend on the final endpoints and treatment groups selected based on phase 2 results.

Phase 3 will be powered and analyzed independently of phase 2, in order to ensure that phase 3 is confirmatory and to avoid inflating type I error rate in phase 3.

Endpoints are listed in Section 3.2.2. Analysis variables are summarized in Section 5.

11.1. Statistical Hypothesis

Phase 1

The safety and tolerability objectives of phase 1 will be evaluated by estimating the proportion of patients with treatment-emergent SAEs through day 29, hypersensitivity reactions (grade ≥2) through day 29, and infusion-related reactions through day 4.

Phase 2

The statistical hypotheses for the primary virologic efficacy endpoint for the phase 2 symptomatic cohort portion of the study are as follows:

- H_0: There is no treatment difference between REGN10933+REGN10987 2400 mg and 8000 mg combined group and placebo in terms of time weighted average change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7
- H_1: There is treatment difference between REGN10933+REGN10987 2400 mg and 8000 mg combined group and placebo in terms of time weighted average change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7

Phase 3

The statistical hypotheses for the primary clinical efficacy endpoint for the phase 3 cohort 1 portion of the study are as follows:

- H_0: The risk of a patient having ≥1 COVID-19-related hospitalization, or all-cause death through day 29 for REGN10933+REGN10987 2400 mg group is the same as that for placebo
- H_1: The risk of a patient having ≥1 COVID-19-related hospitalization, or all-cause death through day 29 for REGN10933+REGN10987 2400 mg group is not the same as that for placebo

11.2. Justification of Sample Size

Phase 2

The sample size for phase 2 is based on the primary virologic endpoint of time-weighted average change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7, using a two-sample t-test at a two-sided significance of α=0.05.

Due to lack of published data on the variation of time-weighted average change from baseline in viral load in COVID-19, the standard deviation of actual viral load values at a timepoint from the literature was used for sample size calculation.

Assuming standard deviation of 2.1 $\log_{10}$ copies/mL (Cao, 2020), a sample size of 20 patients per arm in phase 1 will have at least 80% power to detect a difference of 1.91 $\log_{10}$ copies/mL. The smallest treatment difference that will result in $p<0.05$ is approximately 1.34 $\log_{10}$ copies/mL. A total sample size of 60 patients is planned for phase 1 including patients randomized to placebo and the 2 REGN10933+REGN10987 combination therapy arms.

Assuming that 23% of the patients may have missing baseline values or drop out early, and assuming a standard deviation of 2.1 $\log_{10}$ copies/mL (Cao, 2020), a sample size of 130 patients per arm per cohort in phase 2 will have at least 80% power to detect a difference of 0.84 $\log_{10}$ copies/mL. If a standard deviation of 3.8 $\log_{10}$ copies/mL is assumed (Wang, 2020c), the detectable difference would be 1.51 $\log_{10}$ copies/mL. Based on this per-arm per cohort sample size calculation, a total sample size of approximately 780 patients is needed. This includes 390 patients in the symptomatic and asymptomatic cohorts (randomized to placebo and to the 2 REGN10933+REGN10987 combination therapy doses). For the clinical endpoint of proportion of patients with ≥1 COVID-19-related medically-attended visit, assuming a 30% rate in the control arm, the smallest treatment difference that will result in $p<0.05$ is approximately 11%.

Phase 3 Cohort 1

The sample size of phase 3 cohort 1 is based on having sufficient power to analyze the primary endpoint (Section 4.1) in the modified full analysis set (mFAS; Section 11.3.1).

Based on data from the phase 2 analysis involving the first 799 symptomatic patients enrolled, as well as blinded phase 3 data, the Sponsor assumes an event rate of 3.4% for COVID-19-related hospitalization or all-cause death among patients on placebo in the mFAS (patients with at least 1 risk factor for severe COVID-19 and a positive SARS-CoV-2 RT-qPCR test at baseline), and that 83% of randomized patients will have a positive SARS-CoV-2 RT-qPCR test at baseline.

Table 9 presents estimated number of randomized patients with at least 1 risk factor for severe COVID-19 at each analysis time point for cohort 1 efficacy analysis.

Table 9: Estimated Sample Sizes at Each Analysis Time Point for Phase 3 Patients with ≥1 Risk Factor for Severe COVID-19

	Placebo FAS (mFAS)[1]	**1200 mg** FAS (mFAS)[1]	**2400 mg** FAS (mFAS)[1]	**8000 mg** FAS (mFAS)[1]	**Total** FAS (mFAS)[1]
Pre-Amendment 6 patients	662 (550)	Not applicable	662 (550)	662 (550)	1986 (1650)
Amendment 6/7 randomized by 17 January 2021	841 (698)	841 (698)	841 (698)	N/A	2523 (2094)
Final analysis, 2400 mg vs. placebo (randomized by 17 January 2021)	1503 (1248)		1503 (1248)		
Interim analysis, 1200 mg vs. placebo (randomized by 17 January 2021)	841 (698)	841 (698)			
Amendment 6/7 randomized by 24 February 2021	1352 (1122)	1352 (1122)	1352 (1122)	N/A	4056 (3366)

Final analysis, 1200 mg vs. placebo (randomized by 24 February 2021)	1352 (1122)	1352 (1122)			

[1] FAS estimates only include those in FAS with ≥1 risk factor for severe COVID-19.

The final primary efficacy analysis for the 2400 mg dose group versus placebo comparison will be performed based on patients randomized on or before 17 January 2021, which includes approximately 1503 randomized patients with COVID-19 risk factors per group in the 2400 mg dose group and the placebo group (1248 per group in the mFAS). With this sample size, the study will have approximately 76% power to detect a significant treatment effect in the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death in mFAS at a 2-sided α of 0.05, assuming 3.4% of patients in the placebo group and 1.7% of patients in the 2400 mg group have an event (ie, a 50% reduction with REGN10933+REGN10987 treatment). If there is a greater treatment difference, such as a 60% reduction, the study will have at least 90% power to detect a significant treatment effect in the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death.

The final efficacy analysis of the 1200 mg dose group versus placebo comparison will be performed in approximately 1352 patients with COVID-19 risk factors per dose group (approximately 1122 per dose group estimated in the mFAS), representing the cohort of patients enrolled starting in Protocol Amendment 6 (ie, when the 1200 mg dose was introduced) through February 24, 2021, the last date that enrollment into the placebo group was allowed. This analysis will only include patients who were concurrently randomized to either the 1200 mg dose group or the placebo group. The study will have approximately 72% power to detect a significant treatment effect in the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death in the mFAS at a 2-sided α of 0.05 assuming 3.4% of patients in the placebo group and 1.7% of patient in the 1200 mg group have an event (ie, a 50% reduction). If there is a greater treatment difference, such as a 60% reduction, the study will have approximately 88% power to detect a significant treatment effect in the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death.

From 25 February 2021 onward, the Sponsor plans to randomize up to 1500 patients 1:1 to either the 1200 mg dose group or the 2400 mg dose group, in addition to the patients already enrolled under protocol amendment 6 and protocol amendment 7, to have adequate precision to estimate the difference in the proportion of patients with a COVID-19-related hospitalization or death between the 2 dose groups. For example, assuming an event rate of 1.7% in each group, with a total of approximately 2100 concurrently randomized patients per arm (1744 per arm in mFAS) in 1200 mg and 2400 mg dose groups, a 2-sided 95% confidence interval for the difference will extend approximately 1% from the observed difference. Blinded sample size re-estimation may be performed based on the pooled observed event rates.

EAST v6.0 software was used for sample size calculation.

Phase 3 Cohort 2 and Cohort 3

Up to approximately 180 pediatric patients in cohort 2 is planned with a goal of approximately 52 patients exposed to each dose of study drug, which is considered adequate to describe the drug concentrations over time. In cohort 2, there will be an enrollment of approximately 20 patients

<10 kg (10 per treatment group) and 20 patients between ≥10 kg and <40 kg (10 per treatment group).

In cohort 3, no minimum or maximum enrollment is planned. Cohort 3 will be analyzed descriptively for safety and may be analyzed descriptively for clinical and virologic outcomes.

Note that cohort 2 and cohort 3 may continue to enroll after enrollment of cohort 1 has been completed.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

Phase 1/2 (Symptomatic)

The phase 1/2 portion of the study includes all symptomatic patients up to the 799th randomized symptomatic patient. The full analysis set (FAS) includes all randomized symptomatic patients in phase 1/2 and is based on the treatment allocated (as randomized). The modified full analysis set (mFAS) includes all randomized patients with positive RT-qPCR in NP swab samples at randomization and is based on the treatment allocated (as randomized). The seronegative FAS or seronegative mFAS are defined as all randomized patients with documented seronegative status at baseline in FAS or mFAS, respectively. Both mFAS and FAS will be used for the summaries of demographic and baseline characteristics and analysis of clinical/biomarker endpoints. mFAS will be used for the analysis of all efficacy endpoints, based on the principle that an anti-viral agent would only be anticipated to provide efficacy in patients with measurable virus at baseline. The seronegative mFAS will be used for the analysis of certain virologic endpoints and in descriptive analyses of certain clinical endpoints.

Phase 2 (Asymptomatic)

Full analysis set (FAS), mFAS, and seronegative mFAS for asymptomatic patients are defined similarly as above.

Phase 3 (Cohort 1)

Only patients with COVID-19 symptoms will be included in phase 3. All symptomatic patients from the 800th randomized symptomatic patient will be included in phase 3. For phase 3 cohort 1, the full analysis set (FAS) includes all randomized symptomatic patients and is based on the treatment allocated (as randomized). The FAS includes patients with and without risk factors for severe COVID-19.

The definition of the modified full analysis set (mFAS) for phase 3 is different from phase 2. In phase 3, the mFAS includes all randomized patients with a positive SARS-CoV-2 central lab-determined RT-qPCR test from nasopharyngeal (NP) swab samples at randomization, and with at least one risk factor for severe COVID-19 at baseline. If pre-dose virologic results from the qualitative test are missing, then results from post-dose sample may be used to determine the qualitative PCR status at baseline, as long as the sample was collected within 2 hours after starting the study drug infusion. The mFAS is based on the treatment allocated (as randomized). The seronegative mFAS is defined as all randomized patients with documented seronegative status at baseline in the mFAS.

Both mFAS and FAS will be used for the summaries of demographic and baseline characteristics. The mFAS will be used for the analysis of clinical, symptoms, and virologic endpoints. The seronegative mFAS will be used for the analysis of certain virologic endpoints and in analyses of certain clinical endpoints. Data from patients with no risk factors will be summarized descriptively.

For the analyses of the 1200 mg group comparing to placebo, only patients concurrently randomized (ie, after protocol amendment 6 is implemented) will be included in the above analysis sets.

Phase 3 (Cohort 2)

The FAS includes all randomized patients in phase 3 cohort 2 and is based on the treatment allocated (as randomized). The modified full analysis set (mFAS) includes all randomized patients with positive RT-qPCR in NP swab samples at randomization and is based on the treatment allocated (as randomized). If pre-dose results from the qualitative test are missing, then results from post-dose sample may be used to determine the qualitative PCR status at baseline, as long as the sample was collected within 2 hours after starting the study drug infusion. The seronegative mFAS is defined as all randomized patients with documented seronegative status at baseline in the mFAS.

Phase 3 (Cohort 3)

Data on all patients in cohort 3 will be utilized in the analyses.

11.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any study drug; it is based on the treatment received (as treated). Determination of "as treated" will be based on the actual study drug received on day 1. Demographic and baseline characteristics, treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

11.3.3. Pharmacokinetic Analysis Set

The PK analysis population includes all patients who received any study drug and who had at least 1 non-missing result following the first dose of study drug. Patients will be analyzed based on actual treatment received.

11.3.4. Immunogenicity Analysis Sets

The ADA analysis set (AAS) includes all patients who received study drug and had at least 1 non-missing ADA result from the ADA assay after first dose of the study drug. Patients will be analyzed according to the treatment actually received.

Samples positive in the ADA assay will be characterized further for ADA titers and for the presence of neutralizing antibody (Nab). The NAb analysis set (NAS) includes all patients who received any study drug and who are negative in the ADA assay or with at least one non-missing result in the NAb assay after first dose of the study drug. Patients will be analyzed according to the treatment actually received.

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category.

Stratification factors are provided in Section 8.6.

Statistical analyses will be performed using Statistical Analysis System (SAS) Version 9.4 or higher.

11.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients: informed consent was signed (by the patient if at or above the country's age of legal adulthood, or by patient's parent[s] or legal guardian[s] if below the country's age of legal adulthood)
- The total number of randomized patients: received a randomization number
- The total number of patients who discontinued the study, and the reasons for discontinuation
- The total number of patients who discontinued from study treatment, and the reasons for discontinuation
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics including medical history will be summarized descriptively for each phase by treatment group, and by all patients combined.

11.4.3. Efficacy Analyses

11.4.3.1. Primary Efficacy Analysis

Phase 2

The primary virologic efficacy variable for phase 2 is time-weighted average change from baseline in viral load from day 1 to day 7, as measured by RT-qPCR in NP swab samples for the symptomatic cohort. The estimand for the primary hypothesis is the difference in means between each of the anti-spike SARS-CoV-2 mAb treatments and placebo (as well as pooled doses and placebo). Data collected after use of convalescent serum therapy will be excluded from efficacy analysis. All other available data will be used in the analysis regardless of intercurrent events such as rescue medication or discontinuation, ie, treatment policy approach. Analysis will be performed for patients with baseline viral load $>10^7$ copies/mL in the mFAS, for patients with baseline viral

load >10^6 copies/mL in the mFAS, seronegative mFAS and for mFAS (with serostatus added to the ANCOVA model as a factor).

The analyses will be based on the observed data with no imputation for missing data except the following cases: uncertain viral load values with less than the lower limit of quantification of the PCR assay but with positive qualitative results are imputed with half of lower limit of quantification of the PCR assay; uncertain values with negative RNA are imputed with 0 $\log_{10}$ copies/mL if the reason for the uncertain values is not a failed test. The primary efficacy variable will be calculated using trapezoidal rule, ie, area under the curve for change from baseline at each time point from day 1 to last observation divided by the number of days from day 1 to day of last observation. The variable is analyzed using an Analysis of Covariance (ANCOVA) model with treatment group, country, and risk factor (no risk factor versus at least 1 risk factor) based on clinical database data as fixed effects and baseline viral load and treatment by baseline interaction as covariates.

The least squares means estimates for the time-weighted average mean change from baseline in viral load for each treatment group, as well as the difference between each anti-spike mAb treatment arm and placebo as well as between combined dose group and placebo, will be presented along with the corresponding p-value, standard error, and associated 95% confidence interval. Accompanying descriptive analyses will be provided at the individual timepoints used to calculate the TWA.

At time of writing of protocol amendment 6, phase 2 analyses were complete and the protocol has been updated for consistency with the SAP for phase 2.

Phase 3 Cohort 1

The primary efficacy endpoint for phase 3 cohort 1 is the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29, which will be compared between each dose group and placebo using the stratified Cochran-Mantel-Haenszel (CMH) test with country as a stratification factor. P-values from the stratified CMH test and 95% confidence intervals for the risk ratio and relative risk reduction (1-risk ratio) using Farrington-Manning method will be presented. Exact method for p-values and confidence intervals will be used if the expected frequencies in all cells are not at least 5. The primary analysis will be performed based on mFAS. As key secondary analyses, the same analyses will be performed for patients with high baseline viral load (>10^6 copies/mL) in the mFAS and for seronegative mFAS, and for proportion of patients with a COVID-19-related hospitalization or all-cause death from day 4 through day 29 in the mFAS. The comparison of 1200 mg dose group to placebo will include only the subset of placebo patients concurrently randomized with 1200 mg dose group. Sensitivity and supportive analyses will be described in the SAP.

11.4.3.2. Secondary Efficacy Analysis

Phase 3

The following section describes analyses planned for phase 3 cohort 1. Analysis of asymptomatic patients (phase 2), pediatric patients (phase 3 cohort 2), and pregnant patients (phase 3 cohort 3) will be descriptive and detailed in the SAP.

Phase 3, Cohort 1 Patient-Reported Symptoms Endpoint

Time to COVID-19 symptoms resolution will be analyzed using the stratified log-rank test with randomization strata as stratification factor. The analyses will be performed in the mFAS. Estimates of median times and associated 95% confidence intervals using the Kaplan-Meier method will be reported. The hazard ratio and 95% CI for time to COVID-19 symptoms resolution of COVID-19 symptoms endpoint will be estimated by the Cox regression model with terms for treatment group and randomization strata. The P-value from the stratified log-rank test will be reported. Patients who do not experience resolution of symptoms will be censored at the last observation time point. Patients who died or had COVID-19-related hospitalization prior to day 29 will be censored at day 29. Patients with a baseline raw score ≤3 will be censored at day 0. Patients with missing baseline assessment will not be included in the analysis. Subgroup analyses may be performed among patients with more than one risk factor, with high baseline viral load, or who are seronegative at baseline.

COVID-19 symptoms included in the analysis are as follows: Body aches such as muscle pain or joint pain, Chest pain, Chills, Cough, Diarrhea, Dizziness, Fatigue, Feverish, Headache, Loss of appetite, Loss of taste/smell, Nausea, pressure/tight chest, Red or watery eyes, Runny nose, Shortness of breath/difficulty breathing, Sore throat, Sputum/Phlegm, and Stomachache.

Time to COVID-19 symptoms resolution will be defined as time from randomization to the first day during which the subject scored 'no symptom' (score of 0) on all of the above symptoms except Cough, Fatigue, and Headache, which can be 'mild/moderate symptom' (score of 1) or 'no symptom' (score of 0).

Additional information regarding the SE-C19 scoring instrument is provided in Section 9.2.13.

Phase 3 Cohort 1 Clinical Endpoints

Proportion endpoints such as proportion of patients with a COVID-19-related hospitalization, ER visit, or all-cause death and proportion of patients with a COVID-related MAV or all-cause death will be compared between each dose group and placebo using the stratified Cochran-Mantel-Haenszel (CMH) test with country as a stratification factor. P-values from the stratified CMH test and 95% confidence intervals for risk ratio and relative risk reduction (1-risk ratio) using Farrington-Manning method will be presented. Exact method for p-values and confidence intervals will be used if the expected frequencies in all cells are not at least 5. The analyses will be performed based on observed data for the mFAS for secondary analyses, and for seronegative mFAS and FAS as additional analyses. Similar analysis will be performed for the proportion of patients with a COVID-19-related hospitalization, ER visit, or urgent care visit as well as proportions of patients with each type of COVID-19-related MAV. Risk difference and its 95% confidence interval based on stratified Newcombe method for the proportion endpoints between 1200 mg and 2400 mg dose groups will calculated based on patients concurrently randomized, ie, under protocol amendments 6/7/8, for the mFAS.

Analyses will be performed for the cumulative incidence of patients having a COVID-19-related hospitalization or all-cause death through day 29 based on the time to first COVID-19-related hospitalization or all-cause death using the stratified log-rank test with randomization strata as stratification factor for mFAS. Estimates of cumulative event rate at different time points and associated 95% confidence intervals using the Kaplan-Meier method will be reported. The hazard ratio and its 95% CI for patients having event will be estimated by the Cox regression model with terms for treatment group (2400 mg dose groups versus placebo), and randomization strata. The

p-value from the stratified log-rank test for risk of having events will be reported. Similar analysis will be performed comparing 1200 mg dose group to placebo including only the subset of patients concurrently randomized. A patient who has no COVID-19-related hospitalization will be censored at last known date of contact up to day 29. A patient who dies on or before day 29 will be considered as having an event at the date of death. A patient with multiple COVID-19 related hospitalizations and/or who dies will be counted as having one event. Similar secondary analyses will be performed for cumulative incidence of COVID-19-related hospitalization, ER visit, or all-cause death and cumulative incidence of patients having a COVID-19-related MAV or all cause death through day 29 for the mFAS. Additional landmark analysis for time to event endpoint such as cumulative incidence of COVID-19 related hospitalization or death may be performed if the proportional hazard assumption is considered not valid. Sensitivity analyses will be performed using FAS.

Additional analyses will be performed to examine the relationship between viral load and COVID-19-related MAVs in patients who underwent an intensive sampling schedule. For example, viral load over time will be compared between patients with and without a COVID-19-related MAV.

Virologic Endpoints

For phase 3 cohort 1, virologic analyses will be descriptive. The time-weighted average change from baseline in viral load (log_{10} copies/mL) from day 1 to post-baseline visit timepoints will be analyzed using the same method as the phase 2 primary virologic endpoint based on mFAS for seronegative patients and seropositive patients separately. In cohort 1, the TWA analysis will be limited to patients who were randomized prior to protocol amendment 6. A similar analysis will be performed for mFAS with baseline serostatus as an additional term to the ANCOVA model. The least squares means estimates for the time-weighted average mean change from baseline in viral load for each treatment group, as well as the difference comparing each anti-spike mAb treatment arm versus placebo, will be presented along with the corresponding p-value, standard error, and associated 95% confidence interval. Subgroup analysis of the TWA change from baseline in viral load at each visit will also be performed by baseline viral load categories ($>10^4$ copies/mL, $>10^5$ copies/mL, $>10^6$ copies/mL, $>10^7$ copies/mL).

For phase 2, time to negative RT-PCR results through day 15 for seronegative mFAS will be analyzed using the stratified log-rank test with randomization strata as a stratification factor. Estimates of median times and associated 95% confidence intervals using the Kaplan-Meier method will be reported. The hazard ratio and its 95% CI for time to negative RT-PCR results through day 15 will be estimated by the Cox regression model with terms for treatment group, baseline viral load, treatment by baseline interaction, randomization strata. P-value from the stratified log-rank test for time to negative RT-PCR results through day 15 will be reported. Similar analysis will be performed for the mFAS with baseline serostatus as an additional term to the model.

Proportion endpoints based on observed virologic data will be compared between groups using similar method as the proportion clinical endpoints. The analyses will be performed for seronegative mFAS as well as for mFAS.

To assess the time course of treatment effect in viral load, the change from baseline in viral load (log_{10} copies/mL) at each visit for seronegative mFAS and mFAS will be analyzed using a mixed-

effect model for repeated measures (MMRM) with terms for baseline viral load, randomization strata, treatment, visit, treatment by baseline viral load interaction, baseline viral load by visit interaction, and treatment-by-visit interaction. Within-patient errors will be modeled with an unstructured, heterogeneous autoregressive (1), or compound symmetry covariance matrix in that order if a model does not converge. The least squares means estimates for the mean at each visit and mean change from baseline to each visit as well as the difference of these estimates between treatment arm and placebo will be provided along with the corresponding standard error, p-value, and associated 95% confidence interval. Subgroup analysis of the change from baseline in viral load at each visit will also be performed by baseline viral load categories ($>10^4$ copies/mL, $>10^5$ copies/mL, $>10^6$ copies/mL, $>10^7$ copies/mL).

Phase 2 Patient-Reported Symptom Endpoints (Exploratory)

Time to alleviation or resolution of COVID-19 symptoms endpoints for the symptomatic patients will be analyzed using the stratified log-rank test with randomization strata as stratification factor. The analyses will be performed for seronegative mFAS as well as for mFAS with baseline serostatus as an additional term to the model. Estimates of median times and associated 95% confidence intervals using the Kaplan-Meier method will be reported. The hazard ratio and its 95% CI for time to alleviation or improvement of COVID-19 symptoms endpoints will be estimated by the Cox regression model with terms for treatment group, randomization strata. P-value from the stratified log-rank test will be reported. Subgroup analysis may be performed for patients with more than one risk factor, with high baseline viral load, or are seronegative at baseline.

Analysis for data from asymptomatic patients, pediatric patients, and pregnant patients will be descriptive and detailed in the SAP.

11.4.4. Control of Multiplicity

Phase 1

For phase 1 primary analysis of safety endpoints, no multiplicity adjustment will be applied. The primary virologic efficacy endpoint will be tested at $\alpha = 0.05$.

Primary Phase 2 Analysis of Virologic and Clinical Endpoints

The primary analysis of virologic and clinical endpoints will be conducted at $\alpha = 0.05$ (Table 10). Eight virologic endpoints and 2 clinical endpoints will be tested hierarchically in the following order:

Table 10: Statistical Testing Hierarchy, Primary Phase 2 Analysis

Hierarchy Number	Description
1	Time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 through day 7 in the mFAS patients with baseline viral load $>10^7$ copies/mL for REGN10933+REGN10987 2400 mg and 8000 mg combined group versus placebo (descriptive analysis will be provided for individual timepoints comprising the time-weighted average for this and all subsequent endpoints)

Hierarchy Number	Description
2	Time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 through day 7 in the mFAS patients with baseline viral load $>10^6$ copies/mL for REGN10933+REGN10987 2400 mg and 8000 mg combined group versus placebo
3	Time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 through day 7 in the Seronegative mFAS for REGN10933+REGN10987 2400 mg and 8000 mg combined group versus placebo
4	Time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 through day 7 in the mFAS for REGN10933+REGN10987 2400 mg and 8000 mg combined group versus placebo
5	Time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 through day 7 in the mFAS patients with baseline viral load $>10^7$ copies/mL for REGN10933+REGN10987 8000 mg group versus placebo
6	Time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 through day 7 in the mFAS patients with baseline viral load $>10^7$ copies/mL for REGN10933+REGN10987 2400 mg group versus placebo
7	Time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 through day 7 in the mFAS patients with baseline viral load $>10^6$ copies/mL for REGN10933+REGN10987 8000 mg group versus placebo
8	Time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 through day 7 in the mFAS patients with baseline viral load $>10^6$ copies/mL for REGN10933+REGN10987 2400 mg versus placebo.
9	Proportion of patients with MAVs through day 29 in the mFAS for REGN10933+REGN10987 2400 mg and 8000 mg combined group versus placebo (patients 1 through 799)
10	Proportion of patients with subset of MAVs consisting only of hospitalization or ER visit or urgent care visit through day 29 in the mFAS for REGN10933+REGN10987 2400 mg and 8000 mg combined group versus placebo (patients 1 through 799)

Phase 3

Cohort 1

The primary endpoint and key secondary endpoint will be tested hierarchically (Table 11), adjusting for interim analysis as described below.

Table 11: Statistical Testing Hierarchy, Phase 3 Cohort 1 Analysis

Hierarchy Number	Description
1	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS for REGN10933+REGN10987 2400 mg group versus placebo
2	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS for REGN10933+REGN10987 1200 mg group versus placebo
3	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients with baseline viral load $>10^6$ copies/mL for REGN10933+REGN10987 2400 mg group versus placebo
4	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients who are seronegative at baseline for REGN10933+REGN10987 2400 mg group versus placebo
5	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients with baseline viral load $>10^6$ copies/mL for REGN10933+REGN10987 1200 mg group versus placebo
6	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients who are seronegative at baseline for REGN10933+REGN10987 1200 mg group versus placebo
7	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 through day 29 in the mFAS for REGN10933+REGN10987 2400 mg group versus placebo
8	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 through day 29 in the mFAS for REGN10933+REGN10987 1200 mg group versus placebo
9	Time to COVID-19 symptoms resolution in the mFAS for REGN10933+REGN10987 2400 mg group versus placebo
10	Time to COVID-19 symptoms resolution in the mFAS for REGN10933+REGN10987 1200 mg group versus placebo

The final analysis of the primary efficacy endpoint, ie, proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 for the 2400 mg group versus placebo comparison will be performed based on patients randomized on or before 17 January 2021 in the mFAS, at α level of 0.05.

If the 2400 mg group versus placebo comparison for the primary endpoint is positive, an interim analysis of the primary efficacy endpoint for the 1200 mg group versus placebo comparison (2 in Table 11) will be performed at α level of 0.01 based on patients randomized on or before 17 January 2021 in the mFAS. If the comparison is positive, this analysis will be considered as the final analysis of the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 for the 1200 mg group versus placebo comparison. Final analysis of the primary and key endpoints for comparisons 3 to 10 (Table 11) will then be performed based on patients randomized on or before 17 January 2021 in the mFAS in the hierarchical order above at α level of 0.05.

If the interim analysis of the primary efficacy endpoint for the 1200 mg group versus placebo comparison is negative at α level of 0.01, no tests will be performed for the primary and key endpoints for comparisons 3 to 10 based on patients randomized on or before 17 January 2021. Final analysis of the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 for the 1200 mg group versus placebo comparison (2 in Table 11) and other comparisons 3 to 10 will be performed based on all patients randomized on or before 24 February 2021 and tested hierarchically at an alpha level adjusted based on the information fraction at the interim analysis using Gamma family alpha spending function, eg, at 0.047 level as illustrated in the example in Table 12.

The Gamma family alpha spending function based on the primary endpoint of proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 for the 1200 mg versus placebo comparison will be used to control for type I error for the planned interim and final analyses. The parameter for the Gamma family spending function will be calculated based on the information fraction of the interim analysis, such that the alpha level at the interim analysis is equal to 0.01 and the remaining alpha level is calculated based on the gamma parameter. The information fraction will be determined based on the sample size in the mFAS at the interim analysis and at the final analysis of the primary endpoint for the 1200 mg group versus placebo comparison.

Table 12 provides an example alpha spending boundary for the interim analysis and final analysis of the primary and key secondary endpoints. Under protocol amendment 6and protocol amendment 7 combined, a total of 2524 patients were randomized to the 1200 mg, 2400 mg, and placebo groups on or before 17 January 2021 for the planned interim analysis, and 4056 patients were randomized on or before 24 February 2021 for the final analysis of 1200 mg versus placebo comparisons. With these sample sizes utilized in each analysis, the information fraction is approximately 62% (gamma = -4), assuming the proportions of RT-qPCR-positive patients in the FAS are the same at the interim and final analysis. The resulting overall alpha for the final analysis would then be 0.047.

Table 12: Example Alpha Spending Function for Analysis of Primary Endpoint

Information Time	Value	Overall α for Proportion Analysis = 0.05
62% of the mFAS patients completing day 29	α (2-sided)	0.01
Final analysis	α (2-sided)	0.047

Cohort 2 and Cohort 3

Analysis of cohort 2 and cohort 3 will be descriptive. No multiplicity adjustment will be applied.

11.4.5. Safety Analysis

11.4.5.1. Adverse Events

Definitions

For safety variables, 2 periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before study drug administration
- The observation period is defined as the time of study drug administration to the last study visit

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the observation period.

Analysis

All adverse events reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries by treatment group will include the following:

- The number (n) and percentage (%) of patients with at least 1 treatment-emergent serious adverse events (SAEs) through day 29 by system organ class and PT
- The number (n) and percentage (%) of patients with at least 1 infusion-related reactions (grade ≥2), through day 4 by PT
- The number (n) and percentage (%) of patients with at least 1 hypersensitivity reactions (grade ≥2), through day 29 by PT

For each phase, summaries by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 event by SOC and PT
- SAEs and AESIs by severity (according to the grading scale outlined in Section 10.2.5), presented by SOC and PT
- SAEs and AESIs by relationship to treatment (related, not related), presented by SOC and PT

- Treatment-emergent SAEs and AESIs
- Treatment-emergent grade 3 or 4 AEs (phase 1, phase 3 cohort 2, and phase 3 cohort 3 <18 years only) by SOC and PT

Deaths and other SAEs will be listed and summarized by treatment arm.

11.4.5.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of patients with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized for each clinical laboratory test for all patients and separately for patients in whom the PCSV criterion was normal or missing at baseline.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out of laboratory range values.

11.4.5.3. Treatment Exposure

The number and percentage of patients randomized and exposed to double-blind study drug, and duration of exposure to treatment during the study will be presented by treatment group.

11.4.5.4. Treatment Compliance

Treatment compliance in terms of total dose and infusion interruption will be summarized. The analysis methods will be detailed in the SAP.

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

Phase 1 (Dense Sampling)

The PK parameters may include, but are not limited to C_{max}, C_{max}/dose, t_{max}, and AUC_{last}.

The concentrations of REGN10933 and REGN10987 in serum over time and selected pharmacokinetic parameters will be summarized descriptively for each of the treatment groups.

Phase 2 and Phase 3 (Sparse Sampling)

The concentrations of REGN10933 and REGN10987 in serum over time will be summarized descriptively for each of the treatment groups

11.4.7. Pharmacokinetics and Pharmacokinetics/Pharmacodynamics Analyses

Exposure-response analyses for select efficacy and safety endpoints and/or biomarkers may be performed, as appropriate.

11.4.8. Analysis of Immunogenicity Data

Immunogenicity will be characterized by the ADA and NAb responses and titers observed in patients in the ADA and NAb analysis sets. ADA response categories and titer categories are defined as follows:

ADA Response Categories:

- ADA Negative, defined as ADA negative response in the ADA assays for all time points regardless of any missing samples
- Pre-existing immunoreactivity, defined as either an ADA positive response in the ADA assay response at baseline with all post first dose ADA results negative, or a positive assay response at baseline with all post first dose ADA assay responses less than 9-fold over baseline titer levels.
- Treatment-emergent response, defined as an ADA positive response in the ADA assay post first dose when baseline results are negative or missing.
- Treatment boosted ADA response, defined as a positive response in the ADA assay post first dose that is greater than or equal to 9-fold over baseline titer levels when baseline results are positive

Titer categories (Maximum titer values):

- Low (titer <1,000)
- Moderate (1,000 ≤ titer ≤10,000)
- High (titer >10,000)

The following analysis will be provided:

- Number (n) and percent (%) of ADA-negative patients (pre-existing immunoreactivity or negative in the ADA assay at all time points) by treatment groups
- Number (n) and percent (%) of treatment-emergent ADA positive patients by treatment groups and ADA titer categories and at the
- Number (n) and percent (%) of treatment-boosted ADA positive patients by treatment groups and ADA titer categories

Listing of all ADA titer levels will be provided for patients with pre-existing, treatment-emergent and treatment-boosted ADA response.

The absolute occurrence (n) and percent of patients (%) with NAb status in the NAb analysis set will be provided by treatment groups.

11.5. Interim Analysis

Phase 1/2

An initial phase 1/2 descriptive analysis of data from the first 275 symptomatic patients enrolled in this study was conducted based on a database lock on 23 Sep 2020.

Phase 3

Cohort 1

An interim analysis of the primary and key secondary endpoints for the 1200 mg treatment group will be performed when the final analysis of the primary efficacy endpoint for the 2400 mg treatment group is conducted. Refer to Section 11.4.4 for more information regarding these analyses.

Cohort 2 and 3

An interim descriptive analysis of phase 3 cohort 2 and 3 may be conducted for regulatory purposes when the phase 3 cohort 1 primary analysis is performed.

11.6. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and Sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the Sponsor is responsible for quality assurance to ensure that the study is conducted, and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing) will be maintained and stored at Regeneron (Sponsor).

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, SAEs, baseline findings, medication, medical history) will be done using internationally recognized and accepted dictionaries.

The eCRF data for this study will be collected with an electronic data capture (EDC) Medidata Rave.

12.1.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IWRS system – randomization, study drug supply
- EDC system – data capture – Medidata Rave
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database
- Electronic Clinical Outcome Assessment (eCOA) system – electronic patient diary and patient reported outcomes

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

Regeneron uses a study-specific risk-based approach to study monitoring and oversight, aligned with risk-based quality principles, outlined in ICH E6 (R2) Guideline for Good Clinical Practice. Risk-Based Quality Monitoring (RBQM) methodology focuses on employing a fit-for-purpose monitoring strategy, supported either directly by Regeneron as sponsor, or via our CRO partners. RBQM strategies include reduced source data verification (SDV), targeted source data review (SDR), the use of off-site/remote and triggered on-site monitoring visits, and Centralized Monitoring to identify site level risks and study level trends.

The investigator must allow study related monitoring activities to occur. The study monitors will perform ongoing source data review to verify that data recorded in the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights

of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and eCRF data are timely, accurate and complete.

The investigator must keep all source documents on file with the eCRF. Case report forms and source documents must be available at all times for inspection by authorized representatives of the Sponsor and regulatory authorities.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (eCRFs) within the EDC system by trained site personnel. All required eCRFs must be completed for each and every patient enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor in the eCRFs. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient eCRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the Sponsor and regulatory authorities.

Corrections to the eCRF will be entered in the eCRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

12.3. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the Sponsor regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the Sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the Sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the Sponsor immediately
- Taking all appropriate measures requested by the Sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, eCRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection.

In addition, representatives of the Sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final eCRF that will be provided to the Sponsor.

12.4.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of eCRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the Sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the Sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the Sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

An informed consent form (ICF) can be defined as either a paper consent form or an electronically-delivered consent (eConsent). An eConsent may be provided only where allowable by local laws and regulations and by site policies.

Due to disease severity, quarantine restrictions, and/or other reasons related to COVID-19, it may be necessary to implement temporary or alternative measures to obtain informed consent per procedures outlined in the investigator site file.

Adult Patients

The ICF used by the investigator must be reviewed and approved by the Sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF and documentation of approval must be provided to the Sponsor before study drug will be shipped to the study site.

For patients at or above the legal age of adulthood, it is the responsibility of the investigator or authorized designee (if acceptable by local regulations) to obtain informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient:

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in the presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, or if there are significant changes to the study procedures, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

Patients Under 18 Years of Age (or Under Country's Legal Age of Adulthood)

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

For patients under the legal age of adulthood, it is the responsibility of the investigator or authorized designee (if acceptable by local regulations) to obtain written informed consent from the patient's parent(s) or legal guardian(s) prior to the patient's participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the fullest possible extent in language that the patient's parent(s) or legal guardian(s) can understand. The ICF should be signed and dated by the patient's parent(s) or legal guardian(s) and by the same investigator or designee who explained the ICF.

Local law and site policies must be observed by the investigator in deciding whether the consent of 1 or both parents/guardians is required. If only 1 parent or guardian signs the ICF, the investigator must document the reason the other parent or guardian did not sign.

The investigator (or authorized designee) may also be required to obtain assent from the patient,, as determined by the IRB/EC and in accordance with the local regulations and requirements:

- Patients who can write but cannot read will have the assent form read to them before writing their name on the form
- Patients who can understand but who can neither write nor read will have the assent form read to them by the person obtaining assent, who will sign and date the ICF to confirm that assent was given

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient's parent(s) or legal guardian(s).

13.3. Patient Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number only, on eCRFs or other documents submitted to the Sponsor. Documents that will not be submitted to the Sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the Sponsor database, will be treated in compliance with all applicable laws and regulations. The Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study

- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patient, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the Sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

14. PROTOCOL AMENDMENTS

The Sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

The Sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the Sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Closeout of a Site

The Sponsor and the investigator have the right to close out a site prematurely.

Investigator's Decision

The investigator must notify the Sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the Sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The Sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

19. REFERENCES

Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. Jama 2020; 323(16):1612-1614.

Baum A, Fulton BO, Wloga E, Copin R, Pascal KE, Russo V, et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. Science 2020.

Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med 2020; 382(19):1787-1799.

CDC. Interim Clinical Considerations for Use of mRNA COVID-19 Vaccines Currently Authorized in the United States.Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/clinical-considerations.html. Published 2020a. Accessed 26 Jan 2021.

CDC. Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 — United States, February 12–March 28, 2020. Morbidity and Mortality Weekly Report 2020b; 69(13).

CDC. Prevalence of Obesity Among Adults, by Household Income and Education — United States, 2011–2014. Morbidity and Mortality Weekly Report 2017; 66(50).

CDC. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) — United States, February 12–March 16, 2020. Morbidity and Mortality Weekly Report 2020c; 69(12).

Chen L, Liu HG, Liu W, Liu J, Liu K, Shang J, et al. [Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia]. Zhonghua Jie He He Hu Xi Za Zhi 2020a; 43(0):E005.

Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020b; 395(10223):507-513.

Cui J, Li F,Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol 2019; 17(3):181-192.

Datta PK, Liu F, Fischer T, Rappaport J,Qin X. SARS-CoV-2 pandemic and research gaps: Understanding SARS-CoV-2 interaction with the ACE2 receptor and implications for therapy. Theranostics 2020; 10(16):7448-7464.

Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano LD, et al. Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-June 7, 2020. MMWR Morb Mortal Wkly Rep 2020; 69(25):769-775.

EMA. Treatments and Vaccines for COVID-19: Authorised Medicines. 2021.

FDA. Coronavirus Disease 2019 (COVID-19).FDA. https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19. Published 2021.

Fehr AR,Perlman S. *Coronaviruses: an overview of their replication and pathogenesis*. Methods Mol Biol. 2015: 1-23.

Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020; 382(18):1708-1720.

He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med 2020; 26(5):672-675.

Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020; 181(2):271-280.e278.

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395(10223):497-506.

Iwasaki A,Yang Y. The potential danger of suboptimal antibody responses in COVID-19. Nat Rev Immunol 2020:1-3.

Jiang S, Hillyer C,Du L. Neutralizing Antibodies against SARS-CoV-2 and Other Human Coronaviruses. Trends Immunol 2020; 41(5):355-359.

Kam YW, Kien F, Roberts A, Cheung YC, Lamirande EW, Vogel L, et al. Antibodies against trimeric S glycoprotein protect hamsters against SARS-CoV challenge despite their capacity to mediate FcgammaRII-dependent entry into B cells in vitro. Vaccine 2007; 25(4):729-740.

Kim L, Whitaker M, O'Halloran A, Kambhampati A, Chai SJ, Reingold A, et al. Hospitalization Rates and Characteristics of Children Aged <18 Years Hospitalized with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, March 1-July 25, 2020. MMWR Morb Mortal Wkly Rep 2020; 69(32):1081-1088.

Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. Bmj 2020; 369:m2107.

Korber B, Fischer W, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, et al. Spike mutation pipeline reveals the emergence of a more transmissible form of SARS-CoV-2. bioRxiv 2020:2020.2004.2029.069054.

Lapostolle F, Schneider E, Vianu I, Dollet G, Roche B, Berdah J, et al. Clinical features of 1487 COVID-19 patients with outpatient management in the Greater Paris: the COVID-call study. Intern Emerg Med 2020; 15(5):813-817.

Lewis NM, Chu VT, Ye D, Conners EE, Gharpure R, Laws RL, et al. Household Transmission of SARS-CoV-2 in the United States. Clinical Infectious Diseases 2020.

Li S,Leader S. Economic burden and absenteeism from influenza-like illness in healthy households with children (5-17 years) in the US. Respir Med 2007; 101(6):1244-1250.

Lighter J, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, et al. Obesity in patients younger than 60 years is a risk factor for Covid-19 hospital admission. Clin Infect Dis 2020.

Lindner D, Fitzek A, Bräuninger H, Aleshcheva G, Edler C, Meissner K, et al. Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases. JAMA Cardiology 2020.

Liu L, Wei Q, Lin Q, Fang J, Wang H, Kwok H, et al. Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. JCI Insight 2019; 4(4).

Liu Y, Yan LM, Wan L, Xiang TX, Le A, Liu JM, et al. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect Dis 2020; 20(6):656-657.

Luo F, Liao FL, Wang H, Tang HB, Yang ZQ,Hou W. Evaluation of Antibody-Dependent Enhancement of SARS-CoV Infection in Rhesus Macaques Immunized with an Inactivated SARS-CoV Vaccine. Virol Sin 2018; 33(2):201-204.

Luo X, Zhou W, Yan X, Guo T, Wang B, Xia H, et al. Prognostic value of C-reactive protein in patients with COVID-19. medRxiv 2020:2020.2003.2021.20040360.

Magyarics Z, Leslie F, Bartko J, Rouha H, Luperchio S, Schörgenhofer C, et al. Randomized, Double-Blind, Placebo-Controlled, Single-Ascending-Dose Study of the Penetration of a Monoclonal Antibody Combination (ASN100) Targeting Staphylococcus aureus Cytotoxins in the Lung Epithelial Lining Fluid of Healthy Volunteers. Antimicrob Agents Chemother 2019; 63(8):e00350-00319.

Mizrahi B, Shilo S, Rossman H, Kalkstein N, Marcus K, Barer Y, et al. Longitudinal symptom dynamics of COVID-19 infection. Nat Commun 2020; 11(1):6208.

Nicola M, Alsafi Z, Sohrabi C, Kerwan A, Al-Jabir A, Iosifidis C, et al. The socio-economic implications of the coronavirus pandemic (COVID-19): A review. Int J Surg 2020; 78:185-193.

Ou X, Liu Y, Lei X, Li P, Mi D, Ren L, et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat Commun 2020; 11(1):1620.

Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiology 2020.

Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020.

Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA 2020; 323(20):2052-2059.

Robbie GJ, Zhao L, Mondick J, Losonsky G,Roskos LK. Population pharmacokinetics of palivizumab, a humanized anti-respiratory syncytial virus monoclonal antibody, in adults and children. Antimicrob Agents Chemother 2012; 56(9):4927-4936.

Ruan Q, Yang K, Wang W, Jiang L,Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020:1-3.

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Ann Emerg Med 2006; 47(4):373-380.

Sandoval Y, Januzzi JL, Jr.,Jaffe AS. Cardiac Troponin for the Diagnosis and Risk-Stratification of Myocardial Injury in COVID-19: JACC Review Topic of the Week. J Am Coll Cardiol 2020.

Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. JAMA Pediatr 2020; 174(9):868-873.

Shi L, Wang Y, Wang Y, Duan G,Yang H. Meta-Analysis of Relation of Creatine kinase-MB to Risk of Mortality in Coronavirus Disease 2019 Patients. Am J Cardiol 2020.

Song F, Shi N, Shan F, Zhang Z, Shen J, Lu H, et al. Emerging 2019 Novel Coronavirus (2019-nCoV) Pneumonia. Radiology 2020; 295(1):210-217.

Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, El Burai Felix S, et al. Coronavirus Disease 2019 Case Surveillance - United States, January 22-May 30, 2020. MMWR Morb Mortal Wkly Rep 2020; 69(24):759-765.

Szablewski C, Chang K, Brown M,et al. SARS-CoV-2 Transmission and Infection Among Attendees of an Overnight Camp — Georgia, June 2020. MMWR Morb Mortal Wkly Rep 2020 2020; 69(31):1023-1025.

Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT,Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell 2020; 181(2):281-292.e286.

Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. Jama 2020a; 323(11):1061-1069.

Wang L. C-reactive protein levels in the early stage of COVID-19. Med Mal Infect 2020b; 50(4):332-334.

Wang P, Liu L, Iketani S, Luo Y, Guo Y, Wang M, et al. Increased Resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7 to Antibody Neutralization. bioRxiv 2021:2021.2001.2025.428137.

Wang Q, Zhang L, Kuwahara K, Li L, Liu Z, Li T, et al. Immunodominant SARS Coronavirus Epitopes in Humans Elicited both Enhancing and Neutralizing Effects on Infection in Non-human Primates. ACS Infect Dis 2016; 2(5):361-376.

Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020c; 395(10236):1569-1578.

Weingartl H, Czub M, Czub S, Neufeld J, Marszal P, Gren J, et al. Immunization with modified vaccinia virus Ankara-based recombinant vaccine against severe acute respiratory syndrome is associated with enhanced hepatitis in ferrets. J Virol 2004; 78(22):12672-12676.

Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med 2020.

WHO. Novel Coronavirus (2019-nCoV) Situation Report – 22. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/. Published 2020. Accessed 24 Apr 2020.

Wu Z,McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020.

Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020; 12(1):8.

Yasui F, Kohara M, Kitabatake M, Nishiwaki T, Fujii H, Tateno C, et al. Phagocytic cells contribute to the antibody-mediated elimination of pulmonary-infected SARS coronavirus. Virology 2014; 454-455:157-168.

Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. JAMA 2020; 323(15):1488-1494.

Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, et al. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-October 3, 2020. MMWR Morb Mortal Wkly Rep 2020; 69(44):1641-1647.

Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395(10229):1054-1062.

Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020; 382(8):727-733.

20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol, "A Master Protocol Assessing the Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Patients with COVID-19", and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the Sponsor or a partnership in which the Sponsor is involved. I will immediately disclose it in writing to the Sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the Sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the planned conduct of the study.

Study Title: A Master Protocol Assessing the Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Patients with COVID-19

Protocol Number: R10933-10987-COV-2067

Protocol Version: Amendment 8

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00147230 v1.0

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ESig Approval	[redacted]

Signature Page for VV-RIM-00147230 v1.0 Approved

AMENDMENT HISTORY

Amendment 8

The primary purpose of this amendment is to 1) end randomization to placebo in all phase 3 cohorts, and 2) revise the statistical analysis for cohort 1, including the primary endpoint, key secondary endpoints, hierarchical testing, and plan for interim/final analyses.

Description of Change	Brief Rationale	Section(s)
Phase 3 Randomization		
As of 25 February 2021, patients will no longer be randomized to placebo	Per IDMC recommendation	Table 1 Summary of Main Phase 3 Adaptations Section 6.1.3 Phase 3 Section 8.6 Method of Treatment Assignment
Phase 3 Statistical Analysis		
The following summarizes the planned statistical analysis for phase 3 cohort 1: • The primary endpoint will be proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 • The key secondary endpoints will be proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 to through day 29, and time to COVID-19 symptoms resolution. Symptoms will include a subset of those captured in the SE-C19, as described in the main text • The full analysis set (FAS) includes all randomized patients with COVID-19 symptoms (starting from the 800th symptomatic patient randomized in the study overall), regardless of whether they have risk factors for severe COVID-19 • The modified full analysis set (mFAS) includes all patients in the FAS with detectable SARS-CoV-2 RNA by RT-qPCR in nasopharyngeal swabs at randomization **and** ≥1 risk factor for severe COVID-19. The mFAS will be used to analyze the primary and key secondary endpoints • Concurrent with the final analysis of the primary endpoint for the 2400 mg treatment group, an interim analysis will be conducted on the primary endpoint for the 1200 mg treatment group • A hierarchy is provided for the primary and key secondary endpoints to control for multiplicity, including a Gamma family spending function to control for alpha in the interim and final analyses • Other endpoints, including those assessing emergency room (ER) visits and other medically-attended visits (MAVs), will be evaluated descriptively • Additional minor details were updated for consistency with the planned analysis Details of the revised statistical analysis are provided in the main text.	Primary endpoint changed based on health authority feedback. Other changes implemented to ensure that efficacy assessment of REGN10933 + REGN10987 is conducted with the most clinically-relevant endpoints	Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Section 3.2.1.5 Rationale for Phase 3 Adaptations Table 1 Summary of Main Phase 3 Adaptations Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints Figure 3 Study Flow Diagram, Phase 2 (and Phase 3 Prior to Amendment 6) Figure 4 Study Flow Diagram, Phase 3 (Cohort 1 Patients; Cohort 3 Patients ≥18 Years) Figure 5 Study Flow Diagram, Phase 3 (Cohort 2 Patients; Cohort 3 Patients <18 Years) Section 6.3 Planned Interim Analysis Section 11.1 Statistical Hypothesis Section 11.2 Justification of Sample Size Table 9 Estimated Sample Sizes at Each Analysis Time Point for Phase 3 Patients with ≥1 Risk Factor for Severe COVID-19 Section 11.3.1 Efficacy Analysis Sets Section 11.4.1 Patient Disposition Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis Section 11.4.4 Control of Multiplicity Table 11 Statistical Testing Hierarchy, Phase 3 Cohort 1 Analysis

Description of Change	Brief Rationale	Section(s)
		Table 12 Statistical Testing Hierarchy, Phase 3 Cohort 1 Analysis Section 11.5 Interim Analysis
The full analysis set (FAS) and modified full analysis set (mFAS) will not require that patients be randomized **and treated**; patients who are randomized and not treated will also be considered part of the FAS or mFAS.	Per health authority feedback	Section 11.3.1 Efficacy Analysis Sets
Additional details have been provided to describe the SE-C19 instrument.	To provide additional information related to a key secondary endpoint	Section 9.2.13 Exploratory Patient-Reported Symptoms Table 7 Symptoms Evaluated in the SE-C19 [new]
Clarified that, in total, up to approximately 8500 patients will be enrolled in phase 3 cohort 1.	To ensure an accurate description of planned enrollment	Table 1 Summary of Main Phase 3 Adaptations Section 7.1 Number of Patients Planned
Added an exploratory objective to assess the clinical efficacy of different dose levels of REGN10933 + REGN10987, as measured by COVID-19-related hospitalizations or all-cause death.	To better understand potential differences in clinical efficacy between REGN10933 + REGN10987 dose levels	Section 2.3 Exploratory Objectives
Time to COVID-19 symptoms resolution will be evaluated as an exploratory endpoint in phase 3 cohort 2.	To assess the potential impact of REGN10933 + REGN10987 on COVID-19 symptoms	Section 4.3 Exploratory Endpoints
Safety Assessment		
For patients who are <12 years of age, a phone call will be made within 6 to 8 hours after completing the infusion to collect targeted safety information. A phone call on day 2 is not required. These patients (or their caregivers) should continue to be instructed to contact the site within the first 24 hours post-infusion if they experience any side effects. This change is consistent with a memorandum that was previously provided to study sites.	Per health authority feedback; to ensure appropriate post-infusion monitoring for younger patients <12 years old	Section 6.1.3 Phase 3 Section 9.1.1 Footnotes for the Schedule of Events Tables, #17
Clarified that any SAE resulting in death that occurs prior to study day 169 should be reported, regardless of patient withdrawal or early termination.	To ensure appropriate capturing of vital status	Section 10.1.1 General Guidelines
Other Changes and Clarifications		
For all study phases, the viral sequencing exploratory endpoint has been removed. The exploratory objective has been revised to the following: • To evaluate viral variants at baseline and post-treatment In addition, clarified that the results of viral sequencing will be reported separately from the CSR.	To provide flexibility with respect to planned viral sequencing analyses	Section 2.3 Exploratory Objectives Section 9.2.10.3 Virology
Added exploratory objective for phase 3 cohort 3: • To describe clinical outcomes of patients treated with REGN10933+REGN10987 using various measures of COVID-19-related medically-attended visits or all-cause death	To assess clinical outcomes among patients who are pregnant at randomization	Section 2.3 Exploratory Objectives

Description of Change	Brief Rationale	Section(s)
Clarified that cohort 2 and cohort 3 may continue to enroll after enrollment of cohort 1 has been completed.	To clarify flexibility of enrollment in phase 3 cohorts	Table 1 Summary of Main Phase 3 Adaptations Section 11.2 Justification of Sample Size
In cohort 2, there will be a minimum enrollment of 20 patients <10 kg (10 per treatment group) and 20 patients between ≥10 kg and <40 kg.	Per health authority feedback	Table 1 Summary of Main Phase 3 Adaptations Section 11.2 Justification of Sample Size
The following phase 3 operational clarifications or changes have been made: • Study visits (including phone calls) are not required solely to collect continuously-monitored assessments, if no other assessments are planned on that day. • Study visits are not required on days when only electronic survey data are collected • TEAEs that led to a medically-attended visit will be collected starting on day 1 post-infusion, when applicable (day 1 post dose collection was previously missing from the schedule of events) • In phase 3 cohort 2, vital status was incorrectly marked as a screening assessment. This error has been corrected • On days 60 and 90, the window for EQ-5D-5L (and EQ-5D-Y) assessment is ±3 days. On days 120 and 169, the window is ±7 days	To ensure operational clarity, including avoiding unnecessary study visits and ensuring appropriate capturing of relevant adverse events and concomitant procedures	Section 8.10 Concomitant Medications and Procedures Table 5 Schedule of Events: Phase 3 (Cohort 1 Patients; Cohort 3 Patients ≥18 Years) Table 6 Schedule of Events: Phase 3 (Cohort 2 Patients; Cohort 3 Patients <18 Years) Section 9.1.1 Footnotes for the Schedule of Events Tables, #7, 8, 14
The following changes to concomitant medication recording have been made: • In addition to targeted concomitant medication, concomitant procedures will also be recorded when applicable • In addition to the listed targeted concomitant medications, “any other vaccines” and “oxygen” will also be recorded as applicable	To capture additional clinical information	Section 9.2.4.3 Record Targeted Concomitant Medications and Concomitant Procedures
The following clarification has been made with respect to medically-attended visits related to COVID-19: • During each indicated collection visit (as provided in the schedule of events), all previously unrecorded COVID-19-related medically-attended visits and details will be recorded, beginning from the day of dosing up to and including the day of collection	To ensure appropriate capturing of clinically-relevant information	Section 9.2.3.2 COVID-19-Related Medically-Attended Visit Details
Clarified that cohort 2 **and cohort 3** will only be enrolled where permitted by local requirements.	To provide enrollment flexibility per regional requirements	Table 1 Summary of Main Phase 3 Adaptations Section 7.2.1 Inclusion Criteria, #1
Clarified that in addition to WPAI+CIQ, EQ-5D-5L, and EQ-5D-Y-5L, the return to usual health and return to usual activities surveys will only be administered at sites when regionally available.	To provide operational flexibility	Section 9.1.1 Footnotes for the Schedule of Events Tables, #14
Neutralizing antibody (NAb) analyses will be conducted in phase 2 and phase 3 (all cohorts).	To provide additional assessment of potential for neutralizing antibodies against	Section 4.2 Secondary Endpoints

Description of Change	Brief Rationale	Section(s)
	REGN10933 + REGN10987	
Clarified that assessment of immunogenicity will be a secondary objective for cohort 2 and cohort 3 of phase 3, and that assessment of drug concentration will be a secondary objective for cohort 3 of phase 3; the objectives were previously listed incorrectly as primary objectives.	To ensure accurate descriptions of planned analyses	Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Table 1 Summary of Main Phase 3 Adaptations Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints
The risk-benefit section has been updated to reflect the current Investigator's Brochure (edition 5). This includes the addition of hypersensitivity reactions (including infusion-related reactions and injection site reactions) as an important identified risk. Additional contextual information related to COVID-19 vaccination as a theoretical consideration has also been provided.	To provide current information regarding the potential risks and benefits of REGN10933 + REGN10987	Section 3.3 Risk-Benefit
In light of the increasing number of therapeutic and preventative COVID-19 agents approved or conditionally authorized reference to individual agents has been removed. References to FDA and EMA have been provided as a general resource for currently-available agents.	To ensure current, accurate, and consistent information	Section 1.6 Current Landscape of Therapeutic and Preventative Agents for COVID-19 [deleted] Section 1.6 A Randomized, Placebo-Controlled Study of Anti-SARS-CoV-2 S Protein Monoclonal Antibodies in Ambulatory Patients with COVID-19
Updates to background information, minor clarifications for consistency, and other minor updates (typographical, editorial) were made.	To ensure clarity, accuracy, and consistency	Throughout the document

Amendment 7

The primary purpose of this amendment is to modify the phase 3 portion of the study in response to health authority feedback. Related modifications (eg, with respect to patients who are pregnant) and other clarifications have also been implemented.

Description of Change	Brief Rationale	Section(s)
All-cause death was added to the cohort 1 (≥18 years) primary endpoint (ie, COVID-19-related medically-attended visits **or all-cause death**) and to several secondary endpoints in cohort 1 and cohort 2 (<18 years). The phase 3 sample size was not updated as a result of this change.	Per health authority feedback; to capture an additional event of clinical importance	Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Section 3.2.1.5 Rationale for Phase 3 Adaptations Table 1 Summary of Main Phase 3 Adaptations Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints Section 11.1 Statistical Hypothesis Section 11.2 Justification of Sample Size Section 11.4.3.1 Primary Efficacy Analysis
In cohort 1, additional secondary endpoints were designated as key endpoints, and the statistical hierarchy was updated to control for multiplicity.	To ensure rigorous statistical analysis	Section 4.2 Secondary Endpoints Section 11.4.3.2 Secondary Efficacy Analysis Section 11.4.4 Control for Multiplicity
Patients who are pregnant at randomization, regardless of age, will be enrolled in a separate double-blinded cohort (cohort 3): • Cohort will be randomized 1:1 to REGN10933+REGN1087 1200 mg or 2400 mg, tiered as applicable based on weight • Patients in the cohort will not be randomized to placebo • Randomization will not be stratified • Depending on their age, patients in cohort 3 will follow the cohort 1 (≥18 years) or cohort 2 (<18 years) schedule of events • For patients in cohort 3 who are ≥18 years, additional samples will be collected for drug concentration and immunogenicity assessment • Analysis will be descriptive and will focus on safety and PK	To increase collection of safety and PK information related to REGN10933 + REGN10987 among patients who are pregnant	Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Table 1 Summary of Main Phase 3 Adaptations Section 7.2.1 Inclusion Criteria, #9 Section 9.1.1 Footnotes for the Schedule of Events Tables, #12, 15
The following changes will be made to cohort 2 (and patients <18 years in cohort 3): • Enrollment will be limited to patients who are symptomatic at randomization and have ≥1 risk factor for severe COVID-19 (ie, enrollment is discontinued for asymptomatic patients) • Removed the presence/absence of COVID-19 symptoms as a stratification factor for randomization • Increased the frequency of vital signs assessments performed during and after infusion for patients <12 years old • For patients who are <12 years old, an additional phone call will be made on day 2 (within 24 hours of	Per health authority request; to focus enrollment on patients with highest potential benefit and ensure appropriate safety monitoring during and within 24 hours after study drug administration	Section 3.2.1 Rationale for Study Design Section 3.2.1.5 Rationale for Phase 3 Adaptations Table 1 Summary of Main Phase 3 Adaptations Section 6.1 Study Description and Duration Section 7.1 Number of Patients Planned Section 7.2.1 Inclusion Criteria, #4, 9

Description of Change	Brief Rationale	Section(s)
infusion) for collection of targeted safety information, and these patients (or their caregivers) should be instructed to contact the site within the first 24 hours post-infusion if they experience any side effects. • Clarified that a minimum of 6 patients <10 kg and 6 patients between ≥10 kg and <40 kg will be enrolled		Section 8.6 Method of Treatment Assignment Section 11.2 Justification of Sample Size Section 6.1.3 Phase 3 Figure 5 Study Flow Diagram, Phase 3 (Cohort 2) Section 9.1.1 Footnotes for the Schedule of Events Tables, #6, #17 Table 6 Schedule of Events: Phase 3 (Cohort 2)
In addition to what is currently being collected, the following safety information will be collected in all phase 3 cohorts: • All treatment-emergent adverse events that led to a medically-attended visit (hospitalization, emergency room visit, urgent care visit, physician's office visit, or telemedicine visit), regardless of relatedness to COVID-19, through day 29 • All treatment-emergent serious adverse events and deaths, from day 30 to day 169 • In addition to standard collection of pregnancy outcome information, for newborn infants of patients who were treated in the study and were pregnant at randomization or became pregnant at any time in the study, the incidence and outcome of any SARS-CoV-2 infection will be collected during day 120 and day 169 follow-up phone calls and reported in the pregnancy report form	Per health authority request and for more comprehensive analysis of medically attended visits and the safety profile of REGN10933 + REGN10987	Section 3.2.1 Rationale for Study Design Section 3.2.1.5 Rationale for Phase 3 Adaptations Section 5.3 Safety Variables Section 6.1.3 Phase 3 Table 5 Schedule of Events: Phase 3 (Cohort 1) Table 6 Schedule of Events: Phase 3 (Cohort 2) Section 9.1.1 Footnotes for the Schedule of Events Tables, #7, 16 Section 9.2.4.2 Adverse Event Monitoring Section 9.2.5 Post-Day 29 Follow-up by Phone Section 10.1.1 General Guidelines Section 10.1.3 Events that Require Expedited Reporting to Sponsor
Clarified that viral variants suspected to confer decreased susceptibility to REGN10933 and/or REGN10987 will be evaluated in nonclinical work separate from this protocol.	Per health authority request	Section 9.2.10.3 Virology
Eligibility criteria have been modified to allow planned use of any authorized or approved vaccine for SARS-CoV-2, if (at the time of screening) it is planned **after** 90 days following study drug administration. This screening allowance may be modified as applicable if CDC recommendations change. • Prior use (prior to randomization), current use (at randomization), or planned use (within 90 days of study drug administration or per current CDC recommendations, as applicable) of any authorized or approved vaccine for SARS-CoV-2 is excluded • Prior, current, or future plans to participate in a clinical research study of an investigational vaccine for SARS-CoV-2 is also excluded	Per current CDC recommendations (CDC, 2020a)	Section 7.2.2 Exclusion Criteria, #13, 14
The followings clarifications were made with respect to assessment of women of childbearing potential (WOCBP) and women who are pregnant: • Pregnancy testing at screening must be performed in all WOCBP, regardless of pregnancy status	To ensure accurate information is collected regarding pregnancy	Section 9.2.1.4 Medical History Section 9.2.6 Pregnancy Test for Women of Childbearing Potential Section 10.1.3 Events that Required Expedited Reporting to the Sponsor

Description of Change	Brief Rationale	Section(s)
• Pregnancy or breastfeeding status at screening must be collected as medical history, if applicable • A paper pregnancy report form must be completed for each patient who becomes pregnant or is pregnant at the signing of consent		
Definitions of risk factors for severe COVID-19 were changed as follows: • Cohort 1: clarified that body mass index (BMI) greater than or equal to 30 (not greater than 30) constitutes a risk factor for severe COVID-19 • Cohort 1: clarified that age greater than **or equal to** 50 years constitutes a risk factor for severe COVID-19 • Cohort 2: for patients at least 2 years old, BMI ≥95th percentile for age and sex, based on CDC growth charts, will constitute a risk factor • Cohort 2: added a new risk factor for severe COVID-19 as an inclusion criterion: Any underlying genetic, neurologic, or metabolic condition, or congenital heart disease deemed by the investigator to constitute a risk factor for severe COVID-19 (note that immunocompromised/on immunosuppressive treatment is already considered a risk factor and is accounted for separately)	To clarify risk factors for severe COVID-19 and ensure alignment with CDC guidance, where applicable	Section 3.2.1.5 Rationale for Phase 3 Adaptations Section 7.2.1 Inclusion Criteria, #9
Updated concomitant medications list such that any medication used to treat an adverse event will be recorded	To ensure collection of clinically relevant concomitant medications	Section 9.2.4.3 Record Targeted Concomitant Medications
Clarified that for the screening SARS-CoV-2 diagnostic test, the **sample** must be collected ≤72 hours of randomization. Samples are not valid for screening if collected >72 hours from randomization, even if the test is performed, or results reported, within the 72-hour window.	To ensure appropriate screening for SARS-CoV-2 infection	Section 7.2.1 Inclusion Criteria
Removed language stating that if diagnostic SARS-CoV-2 testing was performed outside of the allowed window, a new test is required for study inclusion. Language was retained in error. Per study exclusion criteria, patients will be excluded if they have a positive SARS-CoV-2 antigen or molecular diagnostic test from a sample collected >72 hours prior to randomization	To ensure accurate information	Section 9.2.1.2 Diagnostic Test for SARS-CoV-2
Provided example of monoclonal antibody (bamlanivimab) that is considered exclusionary for study enrollment	For clarity	Section 7.2.2 Exclusion Criteria, #2, 3
Members of the clinical site study team and their immediate family members are now excluded from enrolling in the study	To ensure integrity of study data and analysis	Section 7.2.2 Exclusion Criteria, #14
In cohort 1, the following blood samples will no longer be collected: • Serum for cytokines and CK-MB • Plasma for hsTroponin Note that the descriptions of exploratory biomarker, analyses, as well as exploratory patient-reported symptom analyses conducted during prior study phases or time periods have been retained in protocol for historical purposes.	To reduce burden of blood sample collections	Table 5 Schedule of Events: Phase 3 (Cohort 1) Section 9.2.10 Exploratory Pharmacodynamic/Biomarker Analyses Section 9.2.13 Exploratory Patient-Reported Symptoms

Description of Change	Brief Rationale	Section(s)
Blood chemistry samples that are collected will not be analyzed for ferritin.	To reduce sample analyses with less relevant clinical significance	Table 5 Schedule of Events: Phase 3 (Cohort 1) Table 6 Schedule of Events: Phase 3 (Cohort 2) Section 9.2.7 Laboratory Testing
Columns have been added to explicitly indicate collection of EQ-5D-5L and EQ-5D-Y-5L at day 60 and day 90. This was previously indicated by a footnote in the schedule of events.	To improve schedule clarity	Section 9.1.1 Footnotes for the Schedule of Events Tables, #14
WPAI+CIQ, EQ-5D-5L, and EQ-5D-Y-5L will only be administered at sites when regionally available.	To provide operational flexibility	Section 9.1.1 Footnotes for the Schedule of Events Tables, #14
Added that an interim analysis of phase 3 cohort 2 may be conducted for regulatory purposes when the phase 3 cohort 1 primary analysis is performed.	To provide more details for the phase 3 statistical analysis plan	Section 11.5 Interim Analysis
Removed incorrectly marked medical history assessment on day 7.	To ensure accuracy	Table 6 Schedule of Events: Phase 3 (Cohort 2)
Removed and/or simplified schedule of events footnotes that contained information relevant to phase 1 and phase 2, which are now closed.	To simplify interpretation of phase 3 schedule of events	Section 9.1.1 Footnotes for the Schedule of Events Tables, #2, 3, 4, 6, 7, 9, 11, 12, 14, 15
Clarified that **approximately** 600 patients will be enrolled in the PK sub-study	To ensure accuracy	Section 9.2.8 Drug Concentration Measurements and Samples
Updated phase 1 endpoint to align with phase 1/2 statistical analysis plan.	To ensure accurate description of statistical analysis that was performed	Section 4.1 Primary Endpoints
Updates to background information and other minor updates were made.	To ensure current, accurate, and consistent information	Throughout the document

Amendment 6

The purpose of this amendment is to adapt the phase 3 portion of the study based on data from phase 1 and phase 2. Major adaptations include changes to the patient population, treatment arms, objectives/endpoints, and sample size.

The following table outlines all changes made to the protocol and the affected sections.

Description of Change	Brief Rationale	Section(s)
Patient Eligibility (Major Phase 3 Adaptation)		
• Females who are pregnant or breastfeeding can enroll in the study • Patients from 0 to <18 years will be enrolled as a separate cohort (cohort 2), where permitted by local requirements. Patients ≥18 years of age will be enrolled in cohort 1 • Patients in cohort 1 must have ≥1 risk factor for severe COVID-19. Patients in cohort 2 must have ≥1 risk factor for severe COVID-19 or live with a housemate who has ≥1 risk factor for severe COVID-19	To adapt the phase 3 portion of the study based on phase 2 data and to evaluate REGN10933 + REGN10987 in younger patients and pregnant/breastfeeding women with COVID-19	Section 3.2.1.5 Rationale for Phase 3 Adaptations [new] Section 5.1 Demographic and Baseline Characteristics Section 6.1 Study Description and Duration Section 7.2.1 Inclusion Criteria, #1, 2, 9 Section 7.2.2 Exclusion Criteria, #10, 11, 12

Description of Change	Brief Rationale	Section(s)
• Patients with a known positive SARS-CoV-2 serology test will be excluded • Patients with a positive SARS-CoV-2 antigen test or molecular diagnostic test from a sample collected >72 hours prior to randomization will be excluded • Patients with active infection with influenza or other non-SARS-CoV-2 respiratory pathogen, confirmed by a diagnostic test, will be excluded *Note: A subset of patients in phase 3 were enrolled prior to the phase 3 adaptations implemented in protocol amendment 6. These patients will not be consented to protocol amendment 6 and will continue to follow the protocol schedule to which they were last consented.*		Section 9.2.5 Post-Day 29 Follow-up by Phone Section 9.2.6 Pregnancy Test for Women of Childbearing Potential Section 10.1.3 Events That Require Expedited Reporting to Sponsor Section 11.4.1 Patient Disposition Section 13.2 Informed Consent
Treatment Arms (Major Phase 3 Adaptation)		
• For cohort 1, the REGN10933+REGN10987 8000 mg IV treatment arm will be dropped. The REGN10933 + REGN10987 2400 mg IV treatment arm and placebo arm will be retained. A new treatment arm will be added to assess REGN10933+REGN10987 1200 mg IV • For cohort 2, the highest dose tested will be REGN10933 + REGN10987 2400 mg IV. Weight-tiered dosing will be used in this cohort	To adapt the phase 3 portion of the study based on phase 2 data	Section 3.2.1.2 Adaptive Master Protocol Design Section 3.2.1.5 Rationale for Phase 3 Adaptations [new] Section 3.2.2 Rationale for Dose Selection Section 6.1.3 Phase 3 [new] Section 8.1 Investigational and Reference Treatments Section 8.6 Method of Treatment Assignments
Objectives/Endpoints (Major Phase 3 Adaptation)		
• For cohort 1, the primary endpoint will be COVID-19-related medically-attended visits (MAVs). Key pre-specified secondary endpoints include various types of COVID-19-related MAVs and related outcomes • For cohort 2, the primary endpoints will be safety/tolerability and drug concentrations in serum over time • For cohort 2, secondary analyses will be descriptive • Virologic analyses for both cohorts will be secondary and descriptive • [redacted]	To adapt the phase 3 portion of the study based on phase 2 data	Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Section 2.3 Exploratory Objectives Section 3.2.1.5 Rationale for Phase 3 Adaptations [new] Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints Section 6.1.3 Phase 3 [new] Table 5 Schedule of Events: Phase 3 (Cohort 1) [new] Table 6 Schedule of Events: Phase 3 (Cohort 2) [new] Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1, Phase 2, and Phase 3), footnote #4 [redacted]

Description of Change	Brief Rationale	Section(s)
Sample Size (Major Phase 3 Adaptation)		
• Enrollment in phase 3 cohort 1 is anticipated to be approximately 5400 patients • Phase 3 cohort 1 will continue until at least 80 hospitalizations or ER visits are observed in patients enrolled under protocol amendment 6 (or subsequent amendment) into the primary analysis population (patients in modified full analysis set [mFAS] with at least 1 risk factor) ***and*** the total number of hospitalizations or ER visits during the study in the primary analysis population is more than 120 • Phase 3 cohort 2 will enroll up to approximately 180 patients	To adapt the phase 3 portion of the study based on phase 2 data	Section 3.2.1.5 Rationale for Phase 3 Adaptations [new] Section 7.1 Number of Patients Planned Section 11.2 Justification of Sample Size
Other Phase 3 Adaptations		
Phase 3 cohort 1 schedule of events will be adapted to include the following major changes from phase 2: • Patients will be followed up by phone on days 120 and 169 (end of study) for assessments including vital status • Virologic assessments will be more limited in scope. Nasopharyngeal (NP) swabs will only be collected on days 1, 7, 15, and 29 • For targeted safety information, treatment-emergent serious adverse events (SAEs), if determined by the investigator to be related to study drug, will be recorded from day 30 to day 169 • A subset of patients will be enrolled in a PK sub-study at selected participating sites. *Note: A subset of patients in phase 3 were enrolled prior to the phase 3 adaptations implemented in protocol amendment 6. These patients will not be consented to protocol amendment 6 and will continue to follow the protocol schedule to which they were last consented.*	Per health authority feedback, and to adapt the phase 3 study design based on phase 2 data	Section 6.1 Study Description and Duration Section 6.1.3 Phase 3 [new] Figure 4 Study Flow Diagram, Phase 3 (Cohort 1) [new] Figure 5 Study Flow Diagram, Phase 3 (Cohort 2) [new] Section 9.2.5 Post-Day 29 Follow-up by Phone Table 5 Schedule of Events: Phase 3 (Cohort 1) [new] Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1, Phase 2, and Phase 3), footnotes #7, 11, 12, 13, 14, 15 Section 9.2.8 Drug Concentration Measurements and Samples Section 10.1.1 General Guidelines Section 10.1.2 Reporting Procedure
Phase 3 cohort 2 will follow similar schedule of events as cohort 1, with key exceptions as follows: • Blood sample collection schedules for laboratory and biomarker analyses will vary according to body weight • Additional NP swab sample will be collected on day 3 • Blood sample collection schedules for pharmacokinetics and immunogenicity will utilize sparse sampling and vary based on randomly assigned sampling schedules • Limited biomarker samples will be collected • Patient-reported electronic surveys/questionnaires will only be collected in patients ≥12 years • Treatment-emergent grade ≥3 AEs will be collected through day 29	To ensure appropriate assessment of safety and efficacy of REGN10933 + REGN10987 and to adjust blood volumes appropriately for younger pediatric patients	Section 6.1.3 Phase 3 [new] 4 Study Flow Diagram, Phase 3 (Cohort 1) [new] Figure 5 Study Flow Diagram, Phase 3 (Cohort 2) [new] Section 7.2.1 Inclusion Criteria, #1a Section 8.1 Investigational and Reference Treatments Section 8.6 Method of Treatment Assignment Table 6 Schedule of Events: Phase 3 (Cohort 2) [new] Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1, Phase 2, and Phase 3), footnotes #7, 11, 13, 14, 15

Description of Change	Brief Rationale	Section(s)
		Section 9.2.5 Post-Day 29 Follow-up by Phone Section 9.2.9 Immunogenicity Measurements and Samples
Details of COVID-19-related medically-attended visits were revised.	To ensure appropriate assessment of the clinical efficacy of REGN10933 + REGN10987	Section 9.2.3.2 COVID-19-Related Medically-Attended Visit Details
Risk factors for hospitalization due to COVID-19 were removed as a stratification factor for randomization. Patients in both cohorts will be stratified by country, and (in cohort 2 only) by the presence or absence of COVID-19 symptoms.	Both cohorts in phase 3 will have ≥1 risk factor for severe COVID-19	Section 8.6 Method of Treatment Assignments
Immunogenicity will be assessed by anti-drug antibodies (ADA) and neutralizing antibody (NAb) analyses, as a secondary endpoint in cohort 1 and a primary endpoint in cohort 2.	To ensure comprehensive assessment of potential immunogenic response following REGN10933 + REGN10987 administration	Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints Section 5.5 Immunogenicity Variables Section 9.2.9 Immunogenicity Measurements and Samples Section 11.3.4 Immunogenicity Analysis Sets Section 11.4.8 Analysis of Immunogenicity Data
Patient eligibility criteria were updated to: • Clarify the acceptable timing for a historical record of positive SARS-CoV-2 test result • Clarify informed consent requirements for cohort 2 patients • Add that patients must be able to understand and complete study-related questionnaires (cohort 1 and cohort 2 patients aged ≥12 years only) • Clarify that patients must not have been admitted to a hospital for COVID-19 prior to randomization, or hospitalized (inpatient) for any reason at randomization • Clarify exclusions related to prior, current, or planned COVID-19 treatments	To ensure appropriate enrollment and data analysis for phase 3 and to provide operational clarity and flexibility	Section 7.2.1 Inclusion Criteria, #2, 6, 8 Section 7.2.2 Exclusion Criteria, #1, 3; #8, 9 [removed]; #10, 11, 12, 13 [added]
For phase 3 cohort 1 efficacy analysis, the Sponsor may request the IDMC to perform 1 or more interim analyses for efficacy	To ensure appropriate assessment of potential efficacy signals	Section 11.5 Interim Analysis
Other Changes and Clarifications		
For patients in this study who are also index cases of household contacts in the R10933-10987-COV-2069 prophylaxis study, data from this study may be used as part of analyses on the COV-2069 study.	To assess the potential impact of REGN10933+REGN10987 treatment of an index case participating in this study on infection rates in household contacts participating in COV-2069.	Section 6.1.3 Phase 3

Description of Change	Brief Rationale	Section(s)
Prior to unblinding for interim analysis of phase 1/2 and analysis of phase 2, changes were made to the statistical analysis plan, including endpoints and analysis descriptions. These changes have been updated in the protocol	To ensure consistency and accuracy of the study statistical plans.	Section 3.2.1.3 Rationale for Phase 1 and Phase 2 Objectives Section 4.1 Primary Endpoints Section 4.2 Secondary Endpoints Section 6.3 Planned Interim Analysis Section 11.5 Interim Analysis
Emergency unblinding procedures were clarified, including manual unblinding in case of IWRS unavailability.	Per health authority request	Section 8.8 Emergency Unblinding
Baseline blood samples may be collected at either day -1 or day 1 (ie, screening or pre-dose) prior to randomization. For patients in phase 3 cohort 2.	To provide operational flexibility.	Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1, Phase 2, and Phase 3), #12
Study monitoring plan was updated to allow off-site/remote monitoring of study sites.	Per health authority request; to provide flexibility for site monitoring due to COVID-19.	Section 12.2.1 Monitoring of Study Sites
Risk-benefit language was updated.	To provide updated risk-benefit information for the program and considerations for a broader patient population	Section 3.3 Risk-Benefit
Descriptions of the statistical plan were updated as follows: • Statistical hypotheses and analysis set definitions were updated • Details regarding control of multiplicity were added • Phase 3 efficacy analysis methods were added • For phase 3, plans for interim analyses were added	To update descriptions of the statistical plan	Section 3.1 Hypotheses Section 6.3 Planned Interim Analysis Section 11 Statistical Plan Section 11.1 Statistical Hypotheses Section 11.3.1 Efficacy Analysis Sets Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis Section 11.4.4 Control of Multiplicity
Descriptions of viral sequencing parameters were updated to expand beyond analyses of potential viral resistance.	For accuracy	Section 9.2.10.3 Virology
Detailed descriptions of exploratory patient-reported symptoms were added.	To provide context for patient-reported symptom assessments	Section 9.2.13 Exploratory Patient-Reported Symptoms
REGN10989 monotherapy will no longer be considered as part of this adaptive master protocol. References to REGN10989 have correspondingly been removed throughout the protocol.	Based on preclinical viral resistance data showing viral escape following monotherapy with anti-SARS-CoV-2 monoclonal antibodies, this study to assess combination therapies and will no longer include monotherapy arms.	Throughout the document

Description of Change	Brief Rationale	Section(s)
References to phase 1 and phase 2 were removed from the study synopsis.	For operational clarity, since phase 1 and phase 2 are now closed	Clinical Study Protocol Synopsis
References to “low dose” and “high dose” were removed.	To ensure clarity with the addition of different dose levels in phase 3	Throughout the document
Updates to background information, administrative updates, and other minor updates to align with phase 3 adaptations were made.	To ensure current, accurate, and consistent information	Throughout the document

Amendment 5

Description of Change	Brief Rationale	Section(s)
Added new cohort of patients in phase 2 to evaluate asymptomatic patients with SARS-CoV-2 infection. Total planned enrollment for phase 2 has been increased to 1300 patients to accommodate this cohort.	To broaden patient eligibility and enable broader assessment of potential treatment impact on viral burden and other measures	Section 3.2.1.3 Rationale for Primary Objectives Section 3.2.1.5 Stratification According to Risk of Hospitalization Due to COVID-19 Section 6.1 Study Description and Duration Section 6.1.2 Phase 2 Figure 3 Study Flow Diagram, Phase 2 Section 7.1 Number of Patients Planned Section 7.2.1 Inclusion Criteria, #4 Section 8.6 Method of Treatment Assignment Section 11.2 Justification of Sample Size Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis
In phase 2, added new secondary clinical endpoint to assess development of symptoms consistent with COVID-19.	To assess the impact of treatment on the development of COVID-19 symptoms in patients who are initially asymptomatic with SARS-CoV-2 infection	Section 4.1 Secondary Endpoints
In phase 2, added new secondary clinical endpoint to assess duration of symptoms consistent with COVID-19.	To assess the impact of treatment on the duration of symptoms	Section 4.1 Secondary Endpoints
Removed screening requirement that patients have ≥1 of the following symptoms at randomization: fever, cough, shortness of breath.	To broaden patient eligibility and to facilitate assessment of potential treatment impact on other clinical manifestations of COVID-19	Section 7.2.1 Inclusion Criteria, #3 [deleted]
At screening, diagnostic testing for SARS-CoV-2 infection will allow antigen tests in addition to molecular tests.	To provide operational flexibility	Section 7.2.1 Inclusion Criteria, #3 Table 4 Schedule of Events: Phase 2 Section 9.2.1.2 Diagnostic Test for SARS-CoV-2
Revised exclusion criteria medications to exclude patients with prior, current, or planned future use of EUA-approved medications (eg, remdesivir), convalescent serum, IVIG, other anti-SARS-CoV2 antibodies, or systemic steroids, thereby allowing antecedent use of other COVID-19 investigational medications such as hydroxychloroquine and azithromycin. Clarified that excluded agents are permitted only if medically indicated.	To broaden patient eligibility	Figure 3 Study Flow Diagram, Phase 2 Section 7.2.2 Exclusion Criteria, #3 Section 7.2.2 Exclusion Criteria, #4 [consolidated with #3], #5, [deleted] Section 8.10.1 Prohibited and Permitted Medications

In phase 2, added blood samples for hematology, blood chemistry, and coagulation tests on days 7 and 15. In phase 2, added blood samples for cardiac biomarkers at baseline and on days 7, 15, and 29.	To enable more comprehensive analysis of safety and efficacy by including additional biomarkers of inflammation and cardiac and/or other organ injury	Section 5.6 Pharmacodynamic and Other Biomarker Variables Section 6.1.2 Phase 2 Table 4 Schedule of Events: Phase 2 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #10 Section 9.2.7 Laboratory Tests Section 9.2.10.8 Serum and Plasma for Cardiac Biomarkers [section added]
Removed post-dose collection of SE-C19 and PGIS and extended daily collection of SE-C19 and PGIS until day 29	To ensure that assessments are only captured once in each 24 hour period , and to provide additional information on patient-reported symptoms at later time points	Table 4 Schedule of Events: Phase 2
Minor clarifications were made to descriptions of other biomarker analyses.	To better describe planned analyses	Section 9.2.10.4 Serological Immunoassays for Anti-SARS-CoV-2 Antibodies Section 9.2.10.5 Serum and Plasma for Research Section 9.2.10.7 Cytokines
Clarified collection of medical history: COVID-19, if applicable, with start date as date of onset of first symptoms.	To ensure appropriate collection of symptom onset	Section 9.2.1.4 Medical History
Information regarding review of sentinel safety group (part A) was added.	To update safety information for the program	Section 3.2.1.1 Phase 1 Sentinel Safety Group
Updated phase 2 interim analysis plans.	To allow flexibility of interim analyses	Section 6.3 Planned Interim Analysis Section 11.4.4 Control of Multiplicity Section 11.5 Interim Analysis
Minor editorial updates made to reflect addition of asymptomatic cohort.	To ensure accuracy and consistency	Section 1.3 Outpatient Care as a Potential COVID-19 Treatment Setting Section 1.6 A Randomized, Placebo-Controlled Study of Anti-SARS-CoV-2 S Protein Monoclonal Antibodies in Ambulatory Patients with COVID-19 or Asymptomatic SARS-CoV-2 Infection Section 3.1 Hypotheses Section 3.2.1 Rationale for Study Design
Removed a duplicate secondary endpoint for phase 3; other minor editorial and administrative updates were made.	To ensure accuracy and consistency	Section 1.1 Emergence of SARS-CoV-2 and COVID-19 Section 4.1 Secondary Endpoints Section 8.6 Method of Treatment Assignment Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #4

Amendment 4

Description of Change	Brief Rationale	Section(s)
Nasal swabs and saliva samples will no longer be collected in phase 2 and are no longer planned for phase 3. Only nasopharyngeal (NP) swabs will be collected in phase 2 and phase 3.	To allow adequate assessment of virologic efficacy, as NP swab is the current gold standard to detect SARS-CoV-2	Clinical Study Protocol Synopsis: Objectives, Study Design, Endpoints, Procedures and Assessments Section 2.2 Secondary Objectives Section 4.1 Secondary Endpoints Section 6.1.2 Phase 2 Figure 2 Study Flow Diagram, Phase 1 Figure 3 Study Flow Diagram, Phase 2 Table 4 Schedule of Events: Phase 2 Section 9.2.3.1 Nasopharyngeal Swab, Nasal Swab, and Saliva Collection Section 11.4.3.2 Secondary Efficacy Analysis
Phase 2 sample size has been increased to enable additional enrollment.	To allow adequate assessment of virologic efficacy	Figure 3 Study Flow Diagram, Phase 2 Section 7.1 Number of Patients Planned Section 11.2 Justification of Sample Size
Interim analysis plan was updated to allow more flexibility in timing.	To allow flexibility of interim analyses	Section 6.3 Planned Interim Analysis Section 9.2.3.1 Nasopharyngeal Swab, Nasal Swab, and Saliva Collection Section 11.5 Interim Analysis
A modified full analysis set (mFAS) was added and includes all randomized patients with a positive RT-qPCR for SARS-CoV-2 in NP swab at randomization.	To allow adequate assessment of virologic efficacy	Section 11.3.1 Efficacy Analysis Sets Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis
An additional secondary virologic endpoint has been added.	To allow adequate assessment of virologic efficacy	Section 4.1 Secondary Endpoints
The following clarifications have been made to the phase 2 Schedule of Events: • Clarified that at concomitant medications are continuously monitored • Visit windows have been added • Removed incorrect vital sign assessments marked in dosing column • Clarified footnote describing phone visit requirements • Day 2 column shading was removed, as day 2 does not include a phone visit	To improve clarity of study schedule	Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #3 Table 4 Schedule of Events: Phase 2

Amendment 3

Description of Change	Brief Rationale	Section(s)
Primary virologic efficacy in phase 2 will be assessed using nasopharyngeal (NP) swab samples. NP swab sample collection has been correspondingly added. Provisional phase 3 secondary endpoints have also been updated for potential inclusion of NP swab samples.	To ensure adequate assessment of virologic efficacy.	Section 2.2 Secondary Objectives Section 4.1 Primary Endpoint Section 4.1 Secondary Endpoints Table 4 Schedule of Events: Phase 2 Section 6.1.2 Phase 2 Section 6.1.3 Phase 3 Figure 3 Study Flow Diagram, Phase 2 Section 9.2.3.1 Saliva, Nasal Swab, and Nasopharyngeal Swab Collection Section 11.4.3.2 Secondary Efficacy Analysis
Additional patients may be enrolled in phase 1 to replace patients who have missing or negative baseline virologic sample(s) or are missing ≥1 follow-up virologic sample(s).	To ensure adequate assessment of virologic efficacy.	Section 7.1 Number of Patients Planned Section 7.4 Replacement of Patients

Amendment 2

Description of Change	Brief Rationale	Section(s)
Grade 3 or 4 treatment-emergent AEs will be collected (phase 1 only)	Per health authority request	Section 3.2.1.3 Rationale for Primary Objectives Section 5.3 Safety Variables Section 6.1.1 Phase 1 Table 3 Schedule of Events: Phase 1 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #7 Section 9.1.3 Unscheduled Visits Section 9.2.4.2 Adverse Event Monitoring Section 10 Safety Evaluation and Reporting (and sub-sections therein) Section 11.4.5.1 Adverse events
Clarified objective, endpoint, and procedure for assessing viral resistance	Per health authority request	Section 2.3 Exploratory Objectives Section 4.3 Exploratory Endpoints Section 9.2.10.3 Virology
Clarified EC and IC terminology related to dose rationale	To clarify in vitro data descriptions	Section 3.2.2 Rationale for Dose Selection
Included secondary objective and endpoint to assess correlations in viral shedding across sample types	To understand differences in assessing virologic efficacy using distinct sampling sources	Section 2.2 Secondary Objectives Section 4.1 Secondary Endpoints Section 11.4.3.1 Primary Efficacy Analysis
Nasopharyngeal swab sampling added to day 11, 15, 18, and 25 (phase 1 only)	To provide matching sample types across time points	Section 6.1.1 Phase 1 Table 3 Schedule of Events: Phase 1 Figure 2 Study Flow Diagram, Phase 1 Figure 3 Study Flow Diagram, Phase 2
Study will be conducted in the US and other countries	To broaden reach of study	Section 6.1 Study Description and Duration

Description of Change	Brief Rationale	Section(s)
Added country as a stratification factor for randomization in phase 2	To ensure balance in study populations	Section 8.6. Method of Treatment Assignment Section 11.4 Statistical Methods
Screening for SARS-CoV-2 infection can be performed by any validated molecular diagnostic assay; historical record ≤72 hours of randomization is acceptable	To clarify acceptable screening criteria	Section 7.2.1 Inclusion Criteria, #2 Table 3 Schedule of Events: Phase 1 Table 4 Schedule of Events: Phase 2 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #5 Section 9.2.1.2 Molecular Diagnostic Test for SARS-CoV-2
For assessment of COVID-19 symptom onset during screening, symptoms are defined per investigator discretion	To clarify inclusion criterion	Section 7.2.1 Inclusion Criteria, #4
Endpoints in phase 1 related to intensive care unit (ICU) and mechanical ventilation moved to exploratory; other statistical clarifications made to primary and secondary efficacy analysis, multiplicity control, and interim analysis	To ensure consistency with planned statistical analysis	Section 4.1 Secondary Endpoints Section 4.3 Exploratory Endpoints Section 11.1 Statistical Hypothesis Section 11.2 Justification of Sample Size Section 11.4.3.2 Secondary Efficacy Analysis Section 11.4.4 Control of Multiplicity Section 11.5 Interim Analysis
Updated study stopping criteria	To provide additional details for study stopping and/or adaptations	Section 6.1.4.2 Study Stopping Criteria
The Independent Data Monitoring Committee (IDMC) will review both safety and efficacy data during the study	To clarify the planned IDMC review process	Section 6.2.1 Independent Data Monitoring Committee
Any unused or leftover biological samples collected during the study may be used for exploratory research; maximum time period of allowable storage ([redacted]) may be shorter per regional laws and regulations	To clarify the intended use and storage of samples	Section 9.2.8 Drug Concentration Measurements and Samples Section 9.2.9 Immunogenicity Measurements and Samples Section 9.2.10 Exploratory Pharmacodynamic/Biomarker Analyses [redacted]
The following operational changes and clarifications have been made: • Phone visits have a window of ±1 day • Day 29 visit may occur at any in-person location • Clarified that home-based visits may be done by home health staff	To provide additional flexibility for sample collection and assessments	Section 6.1.1 Phase 1 Section 6.1.2 Phase 2 Table 3 Schedule of Events: Phase 1 Table 4 Schedule of Events: Phase 2 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #3
Early termination visit will consist of day 29 assessments, with follow-up phone contact on day 29	To clarify early termination assessments	Section 1 Early Termination from the Study
Updated the list of targeted concomitant medications to be recorded	To ensure consistency with eCRF	Section 9.2.4.3 Record Targeted Concomitant Medications

Description of Change	Brief Rationale	Section(s)
Respiratory rate will only be measured in phase 1; temperature will not be measured rectally	To clarify required assessments	Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #6 Section 9.2.4.1 Vital Signs
Updated description of SE-C19 survey	To clarify the scoring system used	Section 9.2.10.8 Exploratory Patient-Reported Symptoms
Removed delineation of visit locations in Schedule of Events; visits may occur at any in-person location except where additional phone visits are indicated	To improve clarity of study schedule and design	Table 3 Schedule of Events: Phase 1 Table 4 Schedule of Events: Phase 2 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #3
Clarifications of study procedures	To improve clarity of procedures and planned analyses	Section 9.2.1.4 Medical History Section 9.2.7 Laboratory Testing Section 9.2.10.2 Serum and Plasma Biomarkers Section 9.2.10.4 Serological Immunoassays for Anti-SARS-CoV-2 Antibodies Section 9.2.10.5 Serum and Plasma for Research Section 9.2.10.4 Complement Section 9.2.10.7 Cytokines
Minor typographical, grammatical, editorial, and formatting updates	To ensure clarity, accuracy, and consistency	Throughout the document

Amendment 1

Description of Change	Brief Rationale	Section(s)
Mandatory sequestering is only applicable to patients in the phase 1 sentinel safety group	Clarification of study design	Section 6.1 Study Description and Duration Figure 2 Study Flow Diagram, Phase 1 Table 3 Schedule of Events: Phase 1 Table 4 Schedule of Events: Phase 2 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #2, #3 Section 9.2.3.2 COVID-19-related Medically-Attended Visit Details
Day 1 vital sign requirements (including pulse oximetry) added for patients in the phase 1 sentinel safety group	Per health authority request	Table 3 Schedule of Events: Phase 1 Table 4 Schedule of Events: Phase 2 Section 9.1.1 Footnotes for the Schedule of Events Tables (Phase 1 and Phase 2), #8
Additional vital sign procedural details provided	To ensure study consistency with health authority request	Section 9.2.4.1 Vital Signs
Independent Data Monitoring Committee (IDMC) description updated	Operational details to be provided in the IDMC charter	Section 6.2.1 Independent Data Monitoring Committee
Editorial updates implemented	To ensure clarity, accuracy, and consistency	Section 8.7 Blinding

STATISTICAL ANALYSIS PLAN
PHASE 3
VERSION: FINAL V1.0

A MASTER PROTOCOL ASSESSING THE SAFETY, TOLERABILITY, AND EFFICACY OF ANTI-SPIKE (S) SARS-COV-2 MONOCLONAL ANTIBODIES FOR THE TREATMENT OF AMBULATORY PATIENTS WITH COVID-19

Compound:	REGN10933+REGN10987 (REGN-CoV2; REGEN-COV)
Protocol Number:	R10933-10987-COV-2067
Clinical Phase:	Phase 1/2/3
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatisticians:	[redacted], [redacted]
Clinical Trial Manager:	[redacted]
Study Medical Directors:	[redacted]
Version/Date:	Original (Version 1.0) / 12 Mar 2021

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

See appended electronic signature page

Study Biostatisticians [redacted])

See appended electronic signature page

Study Medical Director [redacted])

See appended electronic signature page

Study Clinical Pharmacologist [redacted])

See appended electronic signature page

Study Bioanalytical Scientist [redacted])

See appended electronic signature page

Project Biostatistician ([redacted])

See appended electronic signature page

Head of BDM ([redacted])

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
COVID-19	Coronavirus Disease 2019
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRP	C-reactive protein
ECG	Electrocardiogram
FAS	Full Analysis Set
ICH	International Council for Harmonisation
IWRS	Interactive Web Response System
IV	Intravenous
mFAS	Modified full analysis set
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects Model for Repeated Measures
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
OP	Oropharyngeal
NP	Nasopharyngeal
PCR	Polymerase Chain Reaction
PCSV	Potentially Clinically Significant Value
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred Term
RBC	Red Blood Cell
RMST	Restricted Mean Survival Time

Abbreviation	Definition
RNA	Ribonucleic Acid
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SC	Subcutaneous
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper Limit Normal
US	United States (of America)
WBC	White blood cell
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

1. EXECUTIVE SUMMARY

The purpose of the statistical analysis plan (SAP) is to ensure the integrity of the study results by pre-specifying the statistical approaches for the analysis of study data prior to a database lock of this phase 1/2/3 adaptive study R10933-10987-COV-2067 of anti-Spike SARS-CoV-2 monoclonal antibodies in ambulatory patients with COVID-19.

Study R10933-10987-COV-2067 is an adaptive phase 1/2/3, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy and safety of co-administered REGN10933+REGN10987 combination therapy ("REGN10933+REGN10987"; REGN-COV2; REGEN-COV) in outpatient (ie, ambulatory) adults with COVID-19. An initial descriptive analysis of phase 1/2 data from the first 275 patients enrolled in this study was conducted based on a database lock on 23 September 2020. The primary phase 2 analysis was conducted based on a database lock on 24 October 2020, in which virologic efficacy was evaluated in the next 524 patients enrolled in the symptomatic cohort and clinical efficacy was evaluated in the combined analysis groups comprised of the first 799 randomized symptomatic patients. These analyses informed the phase 3 study design and provided insight into how the phase 3 analysis plan should be organized.

This version of the SAP implements the final phase 3 analysis plan for the study according to protocol amendment 8. The phase 3 portion of the study consists of patients separated into 3 cohorts: cohort 1 (symptomatic patients ≥18 years of age after 799 symptomatic patients from phase 1/2, not pregnant at randomization), cohort 2 (<18 years of age, not pregnant at randomization), and cohort 3 (pregnant at randomization). The analyses described herein apply only to the three cohorts in phase 3.

Based on the concept that the effects of REGN10933+REGN10987 are mediated by anti-viral activity and that benefit would be best observed by focusing analyses on patients who had not cleared virus at baseline and are at high risk for severe COVID-19, efficacy analyses will be conducted in a subset of the full analysis set (FAS), termed the modified full analysis set (mFAS), which includes patients who have detectable SARS-CoV-2 RNA by RT-qPCR in nasopharyngeal swabs at randomization and at least 1 risk factor for severe COVID-19. Analyses in the FAS that are not dependent on having detectable virus at baseline will be provided as supportive analysis. (The FAS represents all patients randomized and analyzed as randomized; it is equivalent to the ITT population for this study).

The Independent Data Monitoring Committee (IDMC) recently made a recommendation to stop enrollment into the placebo group based on clear efficacy. The Sponsor stopped enrolling patients in the placebo group as of 25 February 2021, and the study continues to enroll patients 1:1 into either of the REGN10933+REGN10987 treatment arms (1200 mg or 2400 mg). Based on the IDMC's recommendation, the Sponsor has decided to perform the final primary efficacy analysis of the REGN10933+REGN10987 2400 mg treatment group versus placebo, where the primary endpoint will be the proportion of patients with a hospitalization related to COVID-19 or all-cause death. The efficacy analysis will be conducted in phase 3, cohort 1 patients with at least 1 risk factor for severe COVID-19 who were randomized on or before 17 January 2021, with a data cut date of 18 Feburary 2021, ensuring all patients had an opportunity to reach day 29. This will be the final primary efficacy analysis for the REGN10933+REGN10987 2400 mg treatment group compared to placebo because it is estimated that there is sufficient power for the analysis of the

proportion of patients with hospitalization related to COVID-19 or all-cause death endpoint. An interim analysis of the REGN10933+REGN10987 1200 mg treatment versus placebo comparisons using patients randomized on or before 17 January 2021 will also be performed. The final analysis of REGN10933+REGN10987 1200 mg versus placebo comparisons will be based on all phase 3 patients randomized on or before 24 February 2021.

1.1. Background/Rationale

This study is an adaptive phase 1/2/3, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy and safety of co-administered REGN10933+REGN10987 combination therapy ("REGN10933+REGN10987") in outpatient (ie, ambulatory) adults with COVID-19. Treatments referenced in the protocol that were not utilized in the study will not be analyzed and are not discussed in this SAP.

1.2. Study Objectives

1.2.1. Primary Objectives

Cohort 1 (≥ 18 Years, Not Pregnant at Randomization)

- The primary objective of phase 3 is to evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo, as measured by COVID-19-related hospitalizations or all-cause death.

Cohort 2 (< 18 Years, Not Pregnant at Randomization)

- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- To further characterize the concentrations of REGN10933 and REGN10987 in serum over time

Cohort 3 (Pregnant at Randomization)

- To evaluate the safety and tolerability of REGN10933+REGN10987

1.2.2. Secondary Objectives

The secondary objectives of the phase 3 are:

Cohort 1

- To evaluate the impact of REGN10933+REGN10987 on the resolution of self-reported COVID-19 symptoms compared to placebo
- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo using various measures of COVID-19-related medically-attended visits, including COVID-19-related hospitalizations, emergency room visits, or all-cause death
- To describe the virologic effects of REGN10933+REGN10987 compared to placebo

- To evaluate the safety and tolerability of REGN10933+REGN10987 compared to placebo
- To further characterize the concentrations of REGN10933 and REGN10987 in serum over time
- To assess the immunogenicity of REGN10933 and REGN10987

Cohort 2

- To evaluate the clinical efficacy of REGN10933+REGN10987 compared to placebo using various measures of COVID-19-related medically-attended visits, including COVID-19-related hospitalizations or all-cause death
- To describe the virologic effects of REGN10933+REGN10987 compared to placebo
- To assess the immunogenicity of REGN10933 and REGN10987

Cohort 3

- To characterize the concentrations of REGN10933 and REGN10987 in serum over time
- To assess the immunogenicity of REGN10933 and REGN10987

1.2.3. Exploratory Objectives

The exploratory objectives of the phase 3 are:

- To evaluate viral variants at baseline and post-treatment
- To explore the potential association of baseline humoral immune response to SARS-CoV-2 on response to REGN10933+REGN10987
- To evaluate the effects of REGN10933+REGN10987 compared to placebo on generation of a humoral immune response to SARS-CoV-2 (as measured by anti-SARS-CoV-2 N protein)
- To explore the effects of REGN10933+REGN10987 on measures of SARS-CoV-2 infectivity as assessed in experimental laboratory assays
- To explore biomarkers predictive of REGN10933+REGN10987 safety, efficacy, and/or disease progression and COVID-19 clinical outcomes
- To explore the underlying mechanisms of action and biology of REGN10933+REGN10987, SARS-CoV-2, and COVID-19
- To explore relationships between REGN10933+REGN10987 exposure and selected efficacy endpoints, safety endpoints, and/or biomarkers
- To evaluate the impact on self-reported symptoms of REGN10933+REGN10987 compared to placebo
- To assess the clinical efficacy of different dose levels of REGN10933+REGN10987, as measured by COVID-19-related hospitalizations or all-cause death

- To describe the relationship between virologic effects of REGN10933+REGN10987 and risk of COVID-19-related medically-attended visit or all-cause death
- [redacted]
- To evaluate the impact of REGN10933+REGN10987 on the resolution of self-reported COVID-19 symptoms compared to placebo (cohort 2 age ≥12 years)
- To describe the clinical outcomes of patients treated with REGN10933+REGN10987 using various measures of COVID-19-related medically-attended visits, including COVID-19-related hospitalizations or all-cause death (cohort 3)

1.2.4. Modifications from the Statistical Section in the Final Protocol

There is no modification from the statistical section in the protocol amendment 8.

1.2.5. Revision History for SAP Amendments

None.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is an adaptive, phase 1/2/3, randomized, double-blinded, placebo-controlled study to evaluate the efficacy, safety, and tolerability of REGN10933+REGN10987 combination therapy in ambulatory patients (ie, outpatients) with early-stage COVID-19.

In phase 1, only symptomatic patients with COVID-19 were enrolled. In phase 2, symptomatic patients and asymptomatic patients were enrolled into separate cohorts. In phase 3, only symptomatic patients are enrolled. The phase 3 patients are enrolled into the following cohorts.

- cohort 1 (≥ 18 years of age, not pregnant at randomization),
- cohort 2 (< 18 years of age, not pregnant at randomization) and
- cohort 3 (pregnant at randomization).

Cohort 1

Prior to protocol amendment 6, patients were randomized in a 1:1:1 allocation ratio to one of the treatments listed below:

- Co-administered REGN10933+REGN10987 combination therapy, 2400 mg (1200 mg each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 8000 mg (4000 mg each of REGN10933 and REGN10987) IV single dose
- Placebo IV single dose

Randomization was stratified by:

- Presence/absence of COVID-19 symptoms (ie, symptomatic versus asymptomatic cohort). Any asymptomatic patient enrolled are considered to be part of phase 2.
- Country
- Risk factors for severe COVID-19 (no risk factors for severe COVID 19 versus ≥1 risk factor for severe COVID-19).

Starting with Protocol Amendment 6, patients were randomized in a 1:1:1 allocation ratio to one of the treatments listed below, according to a central randomization scheme using an interactive web response system (IWRS) and randomization was stratified by country. The stratification factors for presence/absence of COVID-19 symptoms and risk factors for hospitalization due to COVID-19 were removed because asymptomatic patients and those without risk factors were no longer eligible for the study:

- Co-administered REGN10933+REGN10987 combination therapy, 1200 mg (600 mg each of REGN10933 and REGN10987) IV single dose
- Co-administered REGN10933+REGN10987 combination therapy, 2400 mg (1200 mg each of REGN10933 and REGN10987) IV single dose
- Placebo IV single dose

Starting with protocol amendment 8, cohort 1 will be randomized 1:1 to a single dose of REGN10933+REGN10987 1200 mg IV or REGN10933+REGN10987 2400 mg IV and randomization stratified by country. Patients in this cohort will no longer be randomized to placebo.

Cohort 2

Starting with Protocol Amendment 6, pediatric patients were enrolled into cohort 2, randomized in a 1:1:1 allocation ratio to a single IV dose of REGN10933+REGN10987 at a lower dose level, at a higher dose level, or to placebo, where the exact dose was tiered according to body weight to match REGN10933+REGN10987 2400 mg or REGN10933+REGN10987 1200 mg, as defined in Table 1.

Starting with protocol amendment 8, cohort 2 will be randomized 1:1 to a single IV dose of REGN10933+REGN10987 high dose or REGN10933+REGN10987 low dose, as defined in Table 1. Patients in this cohort will no longer be randomized to placebo.

Table 1: REGN10933+REGN10987 IV Doses for Each Weight Group, Phase 3 Cohort 2 (Ages 0 to <18 Years)

Body Weight Group	Dose Equivalent for REGN10933+REGN10987 1200 mg IV Dose (600 mg per mAb)	Dose Equivalent for REGN10933+REGN10987 2400 mg IV Dose (1200 mg per mAb)
≥40 kg	1200 mg (600 mg per mAb)	2400 mg (1200 mg per mAb)
≥20 kg to <40 kg	450 mg (225 mg per mAb)	900 mg (450 mg per mAb)
≥10 kg to <20 kg	224 mg (112 mg per mAb)	450 mg (225 mg per mAb)
≥5 kg to <10 kg	120 mg (60 mg per mAb)	240 mg (120 mg per mAb)
≥2.5 kg to <5 kg	60 mg (30 mg per mAb)	120 mg (60 mg per mAb)
<2.5 kg	30 mg (15 mg per mAb)	60 mg (30 mg per mAb)

In phase 3 cohort 2, randomization will be stratified by country

Cohort 3

Patients in cohort 3 will be randomized in a 1:1 allocation ratio to co-administered REGN10933+REGN10987 combination therapy IV single dose (no placebo). Patients in cohort 3 who are ≥18 years of age will follow the REGN10933+REGN10987 dose levels described for cohort 1 (1200 mg and 2400 mg). Patients in cohort 3 who are <18 years of age will follow the adjusted REGN10933+REGN10987 dose levels described in Table 1.

In phase 3, cohort 3, randomization will not be stratified.

The study design schematic before protocol amendment 8 is presented in Figure 1 and Figure 2.

Figure 1: Study Flow Diagram, Phase 3 (Cohort 1 Patients; Cohort 3 Patients ≥18 Years)

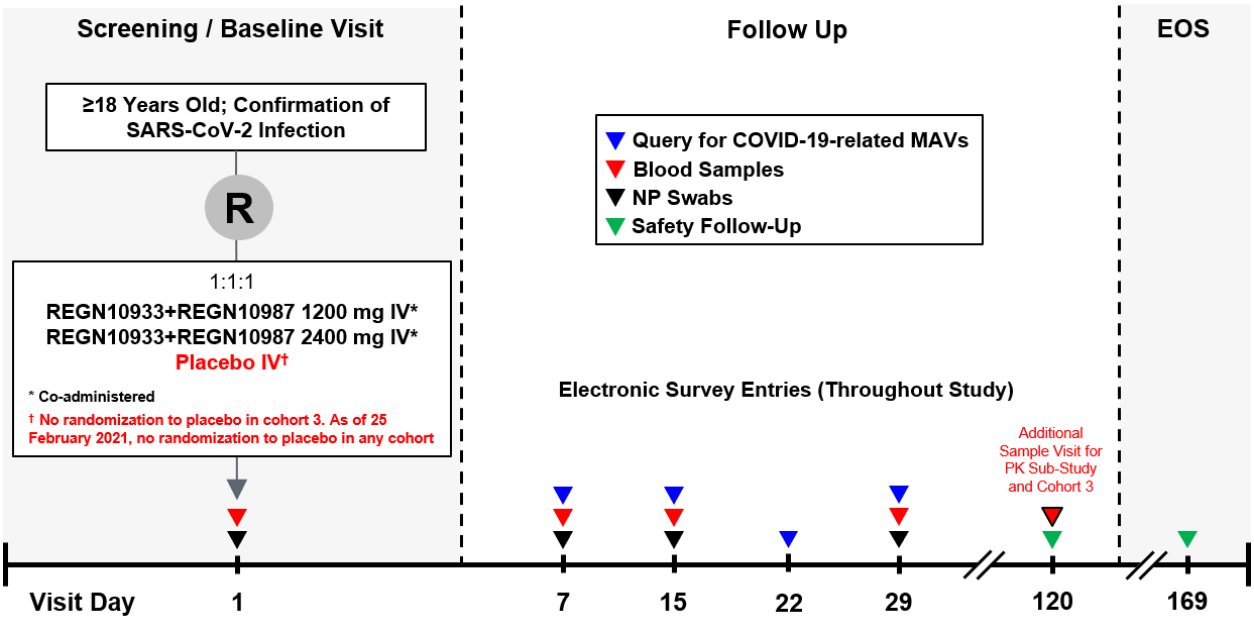
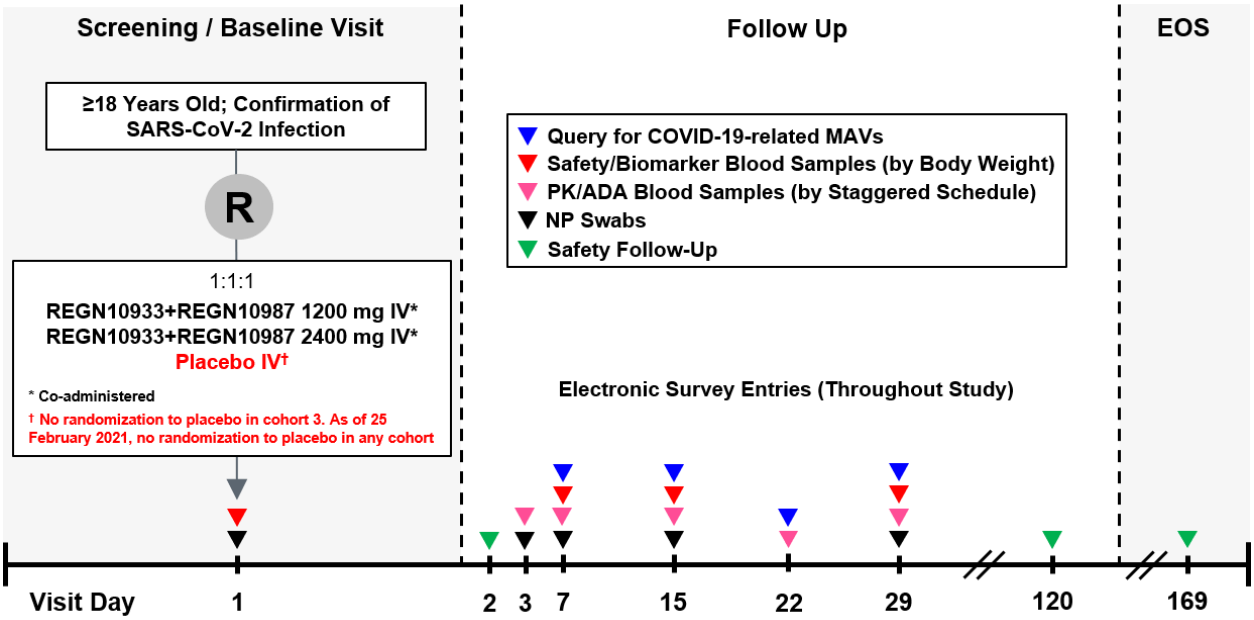


Figure 2: Study Flow Diagram, Phase 3 (Cohort 2 Patients; Cohort 3 Patients <18 Years)



2.2. Sample Size and Power Considerations for Phase 3

The phase 3 sample size of the study is based on having sufficient power to analyze the primary endpoint of proportion of patients with a COVID-19-related hospitalization or all-cause death in the modified full analysis set (mFAS). Based on data from the phase 2 analysis involving the first 799 symptomatic patients enrolled and blinded phase 3 data, the sponsor assumes an event rate of 3.4% for COVID-19-related hospitalization or all-cause death among patients on placebo in the mFAS (patients with at least 1 risk factor for severe COVID-19 and a positive SARS-CoV-2 RT-qPCR test at baseline), and that 83% of all randomized patients (FAS) will have a positive SARS-CoV-2 RT-qPCR test at baseline.

The following table presents estimated number of randomized patients with at least 1 risk factor for severe COVID-19 at each analysis time point for cohort 1 efficacy analysis.

Table 2: Estimated sample sizes at each analysis time point for Phase 3 patients with at least 1 risk factor for severe COVID-19

	Placebo FAS[1] (mFAS)	1200 mg FAS[1] (mFAS)	2400 mg FAS[1] (mFAS)	8000 mg FAS[1] (mFAS)	Total FAS[1] (mFAS)
Pre-Amendment 6 patients	662 (550)	Not applicable	662 (550)	662 (550)	1986 (1650)
Amendment 6/7 patients randomized by 17 January 2021	841 (698)	841 (698)	841 (698)	Not applicable	2523 (2094)
Final analysis for 2400 mg vs. placebo (patients randomized by 17 January 2021)	1503 (1248)		1503 (1248)		
Interim analysis for 1200 mg vs. placebo (patients randomized by 17 January 2021)	841 (698)	841 (698)			
Amendment 6/7 patients randomized by 24 February 2021	1352 (1122)	1352 (1122)	1352 (1122)	Not applicable	4056 (3366)
Final analysis for 1200 mg vs. placebo (patients randomized by 24 February 2021)	1352 (1122)	1352 (1122)			

[1] FAS estimates only include those in FAS with ≥1 risk factor for severe COVID-19.

The final primary efficacy analysis for the 2400 mg dose group versus placebo comparison will be performed based on patients randomized on or before 17 January 2021, which includes approximately 1503 randomized patients with COVID-19 risk factors per group in the 2400 mg dose group and the placebo group (1248 per group in mFAS). The study will have approximately 76% power to detect a significant treatment effect in the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death in mFAS at a 2-sided α of 0.05, assuming 3.4% of

patients in the placebo group and 1.7% of patients in the 2400 mg group have an event (ie, a 50% reduction with R10933+R10987 treatment). If there is a greater treatment difference, such as a 60% reduction, the study will have at least 90% power to detect a significant treatment effect in the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death.

The final efficacy analysis of the 1200 mg dose group versus placebo comparison will be performed in approximately 1352 patients with COVID-19 risk factors per dose group (approximately 1122 per dose group estimated in mFAS), representing the cohort of patients enrolled starting in Protocol Amendment 6 (i.e., when the 1200 mg dose was introduced) through February 24, 2021, the last date that enrollment into the placebo group was allowed. This analysis will only include patients who were concurrently randomized to either the 1200 mg dose group or the placebo group. The study will have approximately 72% power to detect a significant treatment effect in the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death in the mFAS at a 2-sided α of 0.05 assuming 3.4% of patients in the placebo group and 1.7% of patient in the 1200 mg group have an event (i.e., a 50% reduction). If there is a greater treatment difference, such as a 60% reduction, the study will have approximately 88% power to detect a significant treatment effect in the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death.

From 25 February 2021 onward, the Sponsor plans to randomize up to approximately 1500 patients 1:1 to either the 1200 mg dose group or the 2400 mg dose group in addition to the patients enrolled under Amendment 6 or 7, to have adequate precision to estimate the difference in the proportion of patients with a COVID-19-related hospitalization or death between the 2 dose groups. For example, assuming an event rate of 1.7% in each group, with a total of approximately 2100 concurrently randomized patients per arm (1744 per arm in mFAS) in 1200 mg and 2400 mg dose groups, a 2-sided 95% confidence interval for the difference will extend approximately 1% from the observed difference. Blinded sample size reestimation may be performed based on the pooled observed event rates.

The EAST v6.0 software was used for sample size calculation.

Phase 3 Cohort 2 and Cohort 3

Up to approximately 180 pediatric patients in cohort 2 is planned with a goal of approximately 52 patients exposed to each dose of study drug, which is considered adequate to describe the drug concentrations over time. In cohort 2, there will be an enrollment of approximately 20 patients <10 kg (10 per treatment group) and 20 patients between ≥10 kg and <40 kg (10 per treatment group).

In cohort 3, no minimum or maximum enrollment is planned.

Cohorts 2 and 3 will be analyzed descriptively for safety, and may be analyzed descriptively for clinical and virologic outcomes.

Note that cohort 2 and cohort 3 may continue to enroll after enrollment of cohort 1 has been completed.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH, 1998) the following population of analysis will be used for all statistical analyses in the phase 1/2 portion of this study.

3.1. Efficacy Analysis Sets

Cohort 1

All symptomatic patients from the 800th randomized symptomatic patient will be included in the phase 3 portion of the study. The full analysis set (FAS) includes all randomized patients in phase 3 cohort 1, including those with or without risk factors for severe COVID-19, and is based on the treatment allocated (as randomized).

The modified full analysis set (mFAS) for phase 3 includes all randomized patients with a positive central lab-determined RT-qPCR test from nasopharyngeal (NP) swab samples at randomization, and *with at least one risk factor for severe COVID-19 at baseline*. If pre-dose virologic results from the qualitative test are missing, then results from post-dose sample may be used to determine the qualitative PCR status at baseline, as long as the sample was collected within 2 hours after starting the study drug infusion. The mFAS is based on the treatment allocated (as randomized). The seronegative mFAS is defined as all randomized patients with documented seronegative status (eg, SARS-CoV-2 serum antibody negative) at baseline in the mFAS.

Both mFAS and FAS will be used for the summaries of demographic and baseline characteristics. The mFAS will be used for the analysis of clinical, symptoms, and virologic endpoints. The seronegative mFAS will be used for the analysis of certain virologic endpoints and in analyses of certain clinical endpoints. Data from patients with no risk factors will be summarized descriptively.

For the analyses of 1200 mg group comparing to placebo, only patients concurrently randomized (ie, after Protocol Amendment 6 is implemented) will be included.

Cohort 2

The FAS includes all randomized patients in phase 3 cohort 2 and is based on the treatment allocated (as randomized). The modified full analysis set (mFAS) includes all randomized patients with positive RT-qPCR in NP swab samples at randomization and is based on the treatment allocated (as randomized). If pre-dose results from the qualitative test are missing, then results from post-dose sample may be used to determine the qualitative PCR status at baseline, as long as the sample was collected within 2 hours after starting the study drug infusion. The seronegative mFAS is defined as all randomized patients with documented seronegative status at baseline in the mFAS.

Cohort 3

Data on all patients in Cohort 3 (pregnant population) will be utilized in the analyses.

3.2. Safety (SAF) Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any study drug; it is based on the treatment received (as treated). Determination of "as treated" will be based on the actual study drug received on day 1. Demographic and baseline characteristics, treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

3.3. Pharmacokinetics Analysis Sets

The pharmacokinetics (PK) analysis population includes all patients who received any study drug (safety population) and who had at least 1 non-missing result following the first dose of study drug. Patients will be analyzed based on actual treatment received.

3.4. Immunogenicity Analysis Sets

The immunogenicity analysis set is dependent on assay availability.

The anti-drug antibody (ADA) analysis set (AAS) includes all subjects who received any study drug (safety population) and had at least one non-missing ADA result from the ADA assay after first dose of the study drug(s). Subjects will be analyzed according to the treatment actually received.

Samples positive in the ADA assay will be characterized further for ADA titers and for the presence of neutralizing antibody (Nab). The NAb analysis set (NAS) includes all patients who received any study drug and who are either negative in the ADA assay or positive for ADA with at least one non-missing result in the NAb assay after first dose of the study drug. Subjects who are negative for ADA are set to negative in the NAb analysis set

Subjects will be analyzed according to the treatment actually received.

4. ANALYSIS VARIABLES

4.1. Demographics and Baseline Characteristics

Demographic and baseline characteristic variables include the following:

- Age at screening (years)
- Age group (<18, 18 to <65, ≥50, ≥65, ≥75)
- Sex (Male, Female)
- Race (Asian, American Indian/Alaska Native, Black/African American, Native Hawaiian/Other Pacific Islander, White and Other)
- Ethnicity (Hispanic or Latino, Not-Hispanic or Latino)
- Baseline Weight (kg)
- Baseline Height (cm)
- Baseline Body mass index (BMI) (kg/m^2) calculated from weight and height
- Obesity (not obese, BMI <=30 kg/m^2; obese, BMI >30 kg/m^2)
- Risk factor for severe COVID-19, per CRF (no risk factor, ≥1 risk factor)
- Baseline SARS-CoV-2 results from central lab (excluding assessment at screening visit)
- Baseline viral load based on RT-qPCR result (copies/mL as well as log10 copies/mL)
- Baseline viral load categories (>10^7, >10^6, >10^5, etc. copies/mL)
- Baseline qualitative RT-PCR results (positive, negative, other)
- Baseline serostatus (positive, negative, other)

  A patient's serostatus is considered to be positive if any anti-SARS-CoV-2 antibody test (eg, anti-SARS-CoV-2 IgA or IgG) is positive, negative if all available tests are negative, and other if serostatus is not positive or negative (eg, borderline result) or is unknown.
- Baseline C-Reactive Protein (mg/L)
- Time from onset of first COVD-19-related symptom, as determined by the investigator, to randomization (days)

4.2. Medical History

Medical history will include the following:

- COVID-19 with start date as the date of onset of first symptom related to COVID-19
- Risk factors for severe COVID-19/hospitalization due to COVID-19 as defined below
- Whether the patient is receiving oxygen at home by nasal cannula

- Pregnancy or breastfeeding status, if applicable

Risk factors for severe COVID-19 are defined as follows:

a. Age ≥50 years (cohort 1 only)
b. Obesity, defined as:
   BMI ≥30 kg/m^2 **(cohort 1 only)**
   BMI (kg/m2) ≥95th percentile for age and sex based on CDC growth charts **(cohort 2 ≥2 years only)**
c. Cardiovascular disease, including hypertension
d. Chronic lung disease, including asthma
e. Type 1 or type 2 diabetes mellitus
f. Chronic kidney disease, including those on dialysis
g. Chronic liver disease
h. Pregnancy
i. Immunosuppressed, based on investigator's assessment
   Examples include cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anemia, thalassemia, and prolonged use of immune-weakening medications
j. Any underlying genetic condition, neurologic condition, metabolic condition, or congenital heart disease deemed by the investigator to be a risk factor for severe COVID-19 **(cohort 2 only)**

4.3. Prior / Concomitant Medications or Procedures

Medications/Procedures will be recorded from the day of informed consent until the final study assessment (Day 169 or early study discontinuation or death). Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to WHO Drug Dictionary (WHODD) version 202003 or later. Patients will be counted once in all ATC categories linked to the medication.

Prior medications/procedures are: medications taken or procedures performed prior to administration of the study drug.

Concomitant medications/procedures are: medications taken or procedures performed following the first dose of study drug through the final study assessment (Day 169 or early study discontinuation or death). This includes medications taken that started before the study and are ongoing during the study.

Only select concomitant medications will be captured in this trial. The select list of medications include, but are not limited to, corticosteroids, remdesivir, lopinavir-ritonavir, chloroquine, hydroxychloroquine, interferon beta, and convalescent serum. In addition, any concomitant procedures used to treat an adverse event will be captured in this trial.

Analysis of medications data will be focused on the targeted medications (specified in the protocol) that are expected to be reviewed and recorded by sites.

4.4. Rescue Medication/or Prohibited Medication During Study

Patients can receive rescue therapy for COVID-19 per local standard-of-care. Rescue treatments are not provided as part of the study.

Patients are not permitted to receive any medication specified in the exclusion criteria (of the protocol) for study enrollment, unless medically indicated. Patients may otherwise continue their normal regimen of medications and procedures. All data collected on medications/procedures (pre-treatment and concomitant) will be summarized.

4.5. Efficacy Endpoints

4.5.1. Primary Efficacy Endpoint

Cohort 1

The primary clinical efficacy endpoint for phase 3 is the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29.

4.5.2. Secondary Efficacy Endpoints

The secondary endpoints for phase 3 are:

Cohort 1

The key secondary endpoints for phase 3 are

- Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 through day 29
- Time to COVID-19 symptoms resolution.

The other secondary efficacy endpoints for phase 3 are:

- Proportion of patients with ≥1 COVID-19-related hospitalization, emergency room (ER) visit, or all-cause death through day 29
- Proportion of patients with ≥1 COVID-19-related medically-attended visit or all-cause death through day 29
- Proportion of patients with COVID-19 related medically-attended visits by type of visit(s) (hospitalization, ER visit, urgent care, and/or physician's office/telemedicine visit) through day 29
- Proportion of patients with ≥2 COVID-19 related medically-attended visits through day 29
- Cumulative incidence of ≥1 COVID-19-related hospitalization or all-cause death through day 29
- Cumulative incidence of COVID-19-related hospitalizations or ER visits through day 29

- Cumulative incidence of patients with ≥1 COVID-19-related medically-attended visit or all-cause death through day 29
- Days of hospitalization due to COVID-19
- Proportion of patients admitted to an ICU due to COVID-19 by day 29
- Proportion of patients requiring supplemental oxygen due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29
- Total number of COVID-19-related medically-attended visits through day 29
- Time to all-cause death
- All-cause death by day 29, day 120, and day 169
- Time-weighted average change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7, as measured by RT-qPCR in NP swab samples (patients enrolled prior to protocol amendment 6 only)
- Change from baseline in viral load at each visit, as measured by RT-qPCR in NP samples

Cohort 2

The secondary endpoints for phase 3 are:

- Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29
- Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 through day 29
- Proportion of patients with ≥1 COVID-19-related hospitalization, ER visit, or all-cause death through day 29
- Proportion of patients with ≥1 COVID-19-related medically-attended visit or all-cause death through day 29
- Proportion of patients with ≥1 COVID-19-related medically-attended visit by type of visit(s) (hospitalization, ER visit, urgent care, and/or physician's office/telemedicine visit) through day 29
- Proportion of patients with ≥2 COVID-19-related medically-attended visits through day 29
- Cumulative incidence of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29
- Cumulative incidence of patients with ≥1 COVID-19-related hospitalization, ER visit, or all-cause death through day 29
- Cumulative incidence of patients with ≥1 COVID-19-related medically-attended visit or all-cause death through day 29

- Days of hospitalization due to COVID-19
- Proportion of patients admitted to an ICU due to COVID-19 by day 29
- Proportion of patients requiring supplemental oxygen due to COVID-19 by day 29
- Proportion of patients requiring mechanical ventilation due to COVID-19 by day 29
- Total number of COVID-19-related medically-attended visits through day 29
- Time to all-cause death
- All-cause death by day 29, day 120, and day 169.
- Time-weighted average change from baseline in viral load (log_{10} copies/mL) from day 1 to day 7, as measured by RT-qPCR in NP swab samples.
- Change from baseline in viral load at each visit, as measured by RT-qPCR in NP samples
- Immunogenicity, as measured by ADA and NAbs to REGN10933 and REGN10987

Cohort 3

The secondary endpoints for phase 3 are:

- Concentrations of REGN10933 and REGN10987 in serum over time
- Immunogenicity, as measured by anti-drug antibodies and neutralizing antibodies to REGN10933 and REGN10987

Endpoint definitions

Time to COVID-19 symptoms resolution will be defined as time from randomization to the first day during which the subject scored none on all symptoms except fatigue, headache, and cough, which can be mild/moderate or none. Patients with missing baseline assessment will not be included in the analysis.

Time-weighted average of change from baseline viral load in the nasopharyngeal (NP) swab samples from day 1 through day 7 will be calculated for each patient with intensive viral load data collection (ie, those randomized under protocol amendment 5 or earlier) using the linear trapezoidal rule as the area under the curve for change from baseline at each time point divided by the time interval for the observation period. Accompanying descriptive analyses will be provided at the individual timepoints used to calculate the TWA.

For example, the time-weighted average change from baseline in viral load in the nasopharyngeal (NP) swab samples till the last observation day t_k will be calculated using formula

$$TWA_{[0-k]} = [\sum_{i=1}^{k} (t_i - t_{i-1}) * (D_i + D_{i-1})/2]/(t_k - t_0)$$

Where

- *k=11* refers to 11 post-baseline assessments

- D_i is the change from baseline in viral load value (log10 copies/mL) obtained at time t_i, D_0 =0
- t_i is the time (day) for which D_i is measured, such as t_0 = 1 (day) for baseline and $\{t_i\}$ = 3, 5, 7, 9, 11, 13, 15, 18, 22, 25, 29, for i=1 to 11 where the postbaseline assessment is taken.
- If the D_i is not available per protocol or missing due to failed test or other reasons, only the time points with non-missing values will be included into the calculation. For example, we will calculate the TWA till day 7. In this case, data is not available at day 1, 2, 4, and 6 per the protocol schedule of events. Suppose the scheduled assessment result is missing at day 5 due to a failed test but non-missing at day 3 and day 7, then

$$TWA_{[0-7]} = [(t_3 - t_0) * (D_3 + D_0)/2 + (t_7 - t_3) * (D_7 + D_3)/2]/(t_7 - t_0)$$

Baseline is defined as the last non-missing value prior to the study drug infusion. Patients with missing baseline will be excluded from the analysis of virologic endpoints. Virologic data after start of study drug infusion will be used as post-baseline assessments.

4.5.3. Pharmacokinetics

- Concentrations of REGN10933 and REGN10987 in serum and select PK parameters

4.5.4. Immunogenicity

- Immunogenicity as measured by anti-drug antibodies (ADA) to REGN10933 and REGN10987

4.5.5. Exploratory Endpoints

Exploratory endpoints for phase 3 are:

- Viral load over time in patients with and without COVID-19-related medically-attended visits
- Change in WPAI+CIQ over time
- Change in EQ-5D-5L over time
- Time to COVID-19 symptoms resolution (cohort 2 ages ≥12 years)

4.6. Safety Variables

Safety endpoints

- Proportion of patients with treatment-emergent SAEs through day 29
- Proportion of patients with infusion-related reactions (grade ≥2) through day 4
- Proportion of patients with hypersensitivity reactions (grade ≥2) through day 29

4.6.1. Adverse Events and Serious Adverse Events

Serious adverse events and AESIs will be collected according to the Schedule of Events (Section 10.1). All adverse events are to be coded to a "Preferred Term (PT)" and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA version 23.0 or later).

Infusion reactions are defined as any relevant AE that occurs during the infusion or up to day 4.

Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the observation period.

The severity of adverse events (including test findings classified as adverse events) will be graded using the current version of the NCI-CTCAE v5.0 (Division of Cancer Treatment and Diagnosis [DCTD], 2020).

Treatment-emergent SAEs or AESIs not listed in the NCI-CTCAE will be graded according to the scale in Table 3.

Table 3: NCI-CTCAE Severity Grading System for Adverse Events

Grade	Severity	Description
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate	Minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)*
3	Severe	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL†
4	Life-threatening	Life threatening consequences; urgent intervention indicated
5	Death	Death related to adverse events

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
† Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

4.6.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) are AEs (serious or non-serious) of scientific and medical interest specific to this drug program, for which ongoing monitoring and rapid communication by the investigator to the sponsor will be appropriate.

Treatment-emergent adverse events of special interest for this study are grade ≥2 hypersensitivity and grade ≥2 infusion-related reactions and any treatment-emergent adverse event that led to a medically-attended visit (phase 3 only), regardless of whether the visit is related to COVID-19.

4.6.3. Laboratory Safety Variables

The clinical laboratory data consists of blood chemistry (including C-Reactive Protein, liver function tests, creatinine and other), hematology, urinalysis, infection testing, SARS-CoV-2 RT-PCR and other (as specified in the protocol).

Clinical laboratory values will be converted to standard international (SI) units and grouped by function in summary tables. Conventional unit may be provided. Functions are defined as follows:

- Liver function including ALT, AST, alkaline phosphatase, total bilirubin,
- Renal function including creatinine, uric acid,
- Electrolytes including sodium, potassium,
- C-Reactive Protein (CRP),
- Creatine Phosphokinase (CPK)
- Metabolic parameters including total proteins, albumin,
- White blood cells (WBCs) including WBCs count and differential count (neutrophils, lymphocytes, eosinophils, basophils, monocytes),
- Red blood cells (RBCs) and platelets including red blood cells count, hemoglobin, hematocrit and platelets count,
- Coagulation parameters including INR, PT, aPTT
- Other

4.6.4. Vital Signs

Vital signs, including temperature, blood pressure, heart rate, and SpO2 are recorded at multiple time points according to Schedule of Time and Events table (See Section 10.1).

4.7. Pharmacokinetic Variables

The PK variables are the concentrations of REGN10933 andREGN10987 in serum and time when a sample was collected as specified in the Schedule of Events table (please refer to table 10.1 in the appendix). (See Section 10.1).

4.8. Pharmacodynamic and Other Biomarker Variables

Exploratory biomarker variables may be reported outside of the clinical study report (CSR).

4.9. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, NAb status, and time-point/visit. Samples will be collected at the visits as specified in Section 10.1.

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, median, standard deviation (SD), Q1, median, Q3, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics variables given in Section 4.1 will be summarized descriptively by treatment group, and all groups combined using full analysis set (FAS), mFAS and safety set for each cohort.

5.2. Medical History

Medical history will be summarized by SOC and PT and by treatment group and all groups combined using FAS for each cohort.

5.3. Prior / Concomitant Medications or Procedures

Prior or concomitant medications/procedures will be summarized by treatment groups using FAS for each cohort. Summaries will present patient counts (and percentages) for all medications, dictionary coded by WHODRUG, by decreasing frequency of the overall group incidence (or high dose group incidence in tables where the overall is not presented) of ATC followed by ATC level 2, ATC level 4 and preferred term. Focus of the results will be on the list of targeted medications (Section 4.3).

5.4. Prohibited Medications

Number and percentage of patients with prohibited medications will be summarized by treatment groups in the FAS population for each cohort, similar to the concomitant medications.

5.5. Subject Disposition

The following will be provided using FAS and mFAS for each cohort:

- The total number of screened patients: signed the ICF
- The total number of randomized patients: received a randomization number
- The total number of patients who discontinued the study, and the reasons for discontinuation
- The total number of patients who discontinued from study treatment, and the reasons for discontinuation
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A summary of analysis sets including FAS, mFAS, SAF, PK, immunogenicity (ADA), and exploratory biomarkers (Section 3).

5.6. Extent of Study Treatment Exposure and Compliance

5.6.1. Measurement of Compliance

Proportion of patients with fully completed infusions of study drug will be reported as the treatment compliance since the patients will only receive one infusion during the study. Treatment compliance and proportion of patients with infusion interruptions will be summarized by treatment group using descriptive statistics based on the SAF population for each cohort.

5.6.2. Exposure to Investigational Product

Exposure to study drug will be examined for each patient as recorded on the Study Drug Administration-IV CRF. The following variables will be analyzed by treatment group:

- Duration of intravenous infusion
- Total volume of drug administered (units: mL)
- Number of patients with total planned dose administered (yes/no)

  If no, reason for not administration of total planned dose (equipment failure, adverse event, other)
- Number of patients with infusion interruptions

The number and percentage of patients randomized and exposed to double-blind study drug will be presented for each treatment group.

5.7. Analyses of Efficacy Variables

5.7.1. Analysis of Primary Efficacy Variables

Cohort 1

The primary efficacy analysis for the clinical endpoint, proportion of patients with COVID-19-related hospitalization or all-cause death through day 29, will be performed based on the mFAS.

The analyses of proportion of patients with COVID-19-related hospitalization or all-cause death through day 29 will be performed for the following null and alternative statistical hypotheses:

- H_0: The risk of having COVID-19-related hospitalization or all-cause death through day 29 for REGN10933+REGN10987 2400 mg group is the same as that for placebo
- H_1: The risk of having COVID-19-related hospitalization or all-cause death through day 29 for REGN10933+REGN10987 2400 mg group is not the same as that for placebo

The proportion of patients with COVID-19-related hospitalization or all-cause death through day 29 will be compared between each dose group and placebo using the stratified Cochran-Mantel-Haenszel (CMH) test with country as a stratification factor. P-values from the stratified CMH test and 95% confidence intervals for the risk ratio and relative risk reduction (1-risk ratio) using Farrington-Manning method will be presented. Exact method for p-values and confidence intervals

will be used if the expected frequencies in all cells are not at least 5. As key secondary analyses, the same analyses will be performed for the proportion of patients with COVID-19-related hospitalization or all-cause death through day 29 for patients with high baseline viral load (>10^6 copies/mL) in the mFAS and for seronegative mFAS, and for proportion of patients with a COVID-19-related hospitalization or all-cause death from day 4 through day 29 in the mFAS. The comparison of 1200 mg dose group to placebo will include only the subset of placebo patients concurrently randomized with 1200 mg dose group. Sensitivity analyses will be performed using FAS. Additional subgroup analysis will also be performed by baseline serostatus (negative, positive, other) and by baseline viral load categories (>10^4 copies/mL, >10^5 copies/mL, >10^6 copies/mL, >10^7 copies/mL).

5.7.2. Analysis of Secondary Efficacy Variables

Patient-reported symptoms endpoint

Cohort 1

Time to symptoms resolution of COVID-19 symptoms (Fever, Sore throat, Cough, Shortness of breath/difficulty breathing, Chills, Nausea, Diarrhea, Headache, Red/watery eyes, Body aches such as muscle pain, Loss of taste/smell, Fatigue, Loss of appetite, Dizziness, Pressure/tightness in chest, Chest pain, Stomach ache, Runny nose, Sputum/phlegm) will be analyzed using the stratified log-rank test with randomization strata as stratification factor. The analyses will be performed for mFAS. Estimates of median times and associated 95% confidence intervals using the Kaplan-Meier method will be reported. The hazard ratio and its 95% CI for time to symptoms resolution of COVID-19 symptoms endpoint will be estimated by the Cox regression model with terms for treatment group, randomization strata. P-value from the stratified log-rank test will be reported. Subgroup analyses may be performed among patients with more than one risk factor, with high baseline viral load, or who are seronegative at baseline.

Patients who do not experience resolution of symptoms will be censored at the last observation time point. Patients who died or had COVID-19-related hospitalization prior to day 29 will be censored at day 29. Patients with a baseline raw score ≤3 will be censored at day 0. Patients with missing baseline assessment will not be included in the analysis.

Clinical endpoints

Cohort 1

The proportion endpoints, such as proportions of patients with a COVID-19-related hospitalization/ER or all-cause death and proportion of patients with a COVID-related MAV or all-cause death, will be compared between each dose group and placebo using stratified Cochran-Mantel-Haenszel (CMH) test with country as a stratification factor. P-values from the stratified CMH test and 95% confidence intervals for risk ratio and relative risk reduction (1-risk ratio) using Farrington-Manning method will be presented. Exact method for p-values and confidence intervals will be used if the expected frequencies in all cells are not at least 5. The analyses will be performed based on observed data for the mFAS, seronegative mFAS, and FAS. Similar analysis will be performed for the proportion of patients with COVID-19-related hospitalization or ER or urgent care visits as well as proportions of patients with each type of COVID-19-related MAVs. Risk difference and its 95% confidence interval based on stratified Newcombe method for the

proportion endpoints between 1200 mg and 2400 mg dose groups will calculated based on patients concurrently randomized, i.e., under Amendment 6, 7 or 8, for the mFAS.

Analyses will be performed for the cumulative incidence of patients having a COVID-19-related hospitalization or all-cause death through day 29 based on the time to first COVID-19-related hospitalization or all-cause death using the stratified log-rank test with randomization strata (country) as stratification factor for mFAS. Estimates of cumulative event rate at different time points and associated 95% confidence intervals using the Kaplan-Meier method will be reported. The hazard ratio and its 95% CI for patients having event will be estimated by the Cox regression model with terms for treatment group (2400 mg dose groups versus placebo), and randomization strata. The p-value from the stratified log-rank test for risk of having events will be reported. Similar analysis will be performed comparing 1200 mg dose group to placebo including only the subset of patients concurrently randomized. A patient who has no COVID-19-related hospitalization will be censored at last known date of contact up to day 29. A patient who dies on or before day 29 will be considered as having an event at the date of death. A patient with multiple COVID-19 related hospitalization visits and/or who dies will be counted as having one event with time computed at the first event.

Similar secondary analyses will be performed for cumulative incidence of patients having a COVID-19-related hospitalization, ER visit, or all-cause death and cumulative incidence of patients having a COVID-19-related MAV or all cause death through day 29 for the mFAS.

Additional landmark analysis for time to event endpoint such as cumulative incidence of hospitalization or death may be performed if the proportional hazard assumption is considered not valid.

Sensitivity analyses will be performed using FAS.

Additional analyses will be performed to examine the relationship between viral load and COVID-19-related MAVs in patients who underwent an intensive sampling schedule. Viral load over time will be compared between patients with and without a COVID-19-related MAV.

Cohort 2 and 3

Proportion of patients with COVID-19-related hospitalization or ER or urgent care visits or all-cause death as well as proportions of patients with each type of MAVs for cohort 1 patients with no risk factor, cohort 2 and 3 will be descriptively summarized.

Virologic endpoints

Cohort 1

For phase 3, virologic analyses will be descriptive.

To assess the time course of treatment effect in viral load, the change from baseline in viral load (log_{10} copies/mL) at each visit for mFAS will be analyzed using a mixed-effect model for repeated measures (MMRM) with terms for baseline viral load, baseline serostatus, country, treatment, visit, treatment by baseline viral load interaction, baseline viral load by visit interaction, and treatment-by-visit interaction. Within-patient errors will be modeled with an unstructured, heterogeneous autoregressive (1), or compound symmetry covariance matrix in that order if a model does not converge. The least squares means estimates for the mean at each visit and mean change from

baseline to each visit as well as the difference of these estimates between each treatment arm and placebo will be provided along with the corresponding standard error, p-value, and associated 95% confidence interval. Subgroup analysis of the change from baseline in viral load at each visit will also be performed by baseline serostatus (negative, positive, other) and by baseline viral load categories (>10^4 copies/mL, >10^5 copies/mL, >10^6 copies/mL, >10^7 copies/mL).

The time-weighted average change from baseline in viral load (log10 copies/mL) from day 1 to post-baseline visit timepoints will be analyzed using the same method as the phase 2 primary virologic endpoint (see Phase 2 primary anlysis SAP) based on mFAS for seronegative patients and seropositive patients separately. This analysis will only be performed for patients randomized prior to amendment 6. The variable is analyzed using an Analysis of Covariance (ANCOVA) model with treatment group and country as fixed effects and baseline viral load and treatment by baseline viral load interaction as covariates. Similar analysis will be performed for mFAS with baseline serostatus as an additional term to the ANCOVA model. The least squares means estimates for the time-weighted average mean change from baseline in viral load for each treatment group, as well as the difference comparing each anti-spike mAb treatment arm versus placebo, will be presented along with the corresponding p-value, standard error, and associated 95% confidence interval. Subgroup analysis of the TWA change from baseline in viral load at each visit will also be performed by baseline viral load categories (>10^4 copies/mL, >10^5 copies/mL, >10^6 copies/mL, >10^7 copies/mL).

Proportion endpoints based on observed virologic data will be compared between groups using similar method as the proportion clinical endpoints based on mFAS.

Cohort 2 and 3

Virologic data for cohort 1 patients with no risk factor, cohort 2 and 3 will be summarized descriptively.

5.7.3. Adjustment for Multiple Comparisons

Cohort 1

The analysis of the primary endpoint (proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29) and key secondary endpoint (time to symptom resolution) will be conducted at the overall $\alpha = 0.05$. The endpoints will be tested hierarchically in the following order, adjusting for interim analysis.

Table 4: Hierarchical testing order

Hierarchy Number	Description
1	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS for REGN10933+REGN10987 2400 mg group versus placebo
2	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS for REGN10933+REGN10987 1200 mg group versus placebo
3	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients with baseline viral load $>10^6$ copies/mL for REGN10933+REGN10987 2400 mg group versus placebo
4	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients who are seronegative at baseline for REGN10933+REGN10987 2400 mg group versus placebo
5	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients with baseline viral load $>10^6$ copies/mL for REGN10933+REGN10987 1200 mg group versus placebo
6	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 in the mFAS patients who are seronegative at baseline for REGN10933+REGN10987 1200 mg group versus placebo
7	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 through day 29 in the mFAS for REGN10933+REGN10987 2400 mg group versus placebo
8	Proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death from day 4 through day 29 in the mFAS for REGN10933+REGN10987 1200 mg group versus placebo
9	Time to COVID-19 symptoms resolution in the mFAS for REGN10933+REGN10987 2400 mg group versus placebo
10	Time to COVID-19 symptoms resolution in the mFAS for REGN10933+REGN10987 1200 mg group versus placebo

The final analysis of the primary efficacy endpoint, i.e., proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 for the 2400 mg group versus placebo comparison will be performed based on patients randomized on or before 17 January 2021 in the mFAS, at α level of 0.05.

If the 2400 mg group versus placebo comparison for the primary endpoint is positive, an interim analysis of the primary efficacy endpoint for the 1200 mg group versus placebo comparison (#2 in Table 4) will be performed at α level of 0.01 based on patients randomized on or before 17 January 2021 in the mFAS. If the comparison is positive, this analysis will be considered as the final analysis of the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 for the 1200 mg group versus placebo comparison. Final analysis of the primary and key endpoints for the comparisons 3 to 10 (Table 4) will be performed based on

patients randomized on or before 17 January 2021 in the mFAS in the hierarchical order above at α level of 0.05.

If the interim analysis of the primary efficacy endpoint for the 1200 mg group versus placebo comparison (#2 in Table 4) is negative at α level of 0.01, no tests will be performed for the primary and key endpoints for the comparisons 3 to 10 in Table 4 based on patients randomized on or before 17 January 2021. Final analysis of the proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 for the 1200 mg group versus placebo comparison (#2 in Table 4) and other comparisons 3 to 10 will be performed based on all patients randomized on or before 24 February 2021 and tested hierarchically at an alpha level adjusted based on the information fraction at the interim analysis using Gamma family alpha spending function, e.g., at 0.047 level as illustrated in the example in Table 5. Additional details are provided in section 7.

Table 5 provides an example alpha spending boundary for the interim analysis and final analysis of the primary and key secondary endpoints. Under amendment 6 and 7, a total of 2524 patients were randomized to the 1200 mg, 2400 mg, and placebo groups on or before 17 January 2021 for the planned interim analysis, and 4056 patients were randomized on or before 24 February 2021 for the final analysis of 1200 mg versus placebo comparisons. With these sample sizes utilized in each analysis, the information fraction is approximately 62% (gamma=-4), assuming the proportions of RT-qPCR-positive patients in the FAS are the same at the interim and final analysis. The resulting overall alpha for the final analysis would then be 0.047 if the interim analysis is negative at 0.01 level.

Table 5: Example Alpha Spending Function for Analysis of Primary Endpoint

Information Time	Value	Overall α for Proportion Analysis = 0.05
62% of the mFAS patients completing day 29	α (2-sided)	0.01
Final analysis	α (2-sided)	0.047

Cohort 2 and 3

Analysis cohort 2 and cohort 3 will be descriptive. No multiplicity adjustment will be applied.

5.8. Analysis of Safety Data

The analysis of safety data will be performed on the SAF, as defined in Section 3.2.

The safety analysis will be based on the reported SAEs and AESIs and other safety information (clinical laboratory evaluations and vital signs).

Thresholds for Potential Clinically Significant Values (PCSV) in laboratory variables, vital signs and ECG are defined in Section 10.2.

The summary of safety results will be presented for each treatment group for each cohort.

5.8.1. Adverse Events

Definitions

For safety variables, 2 periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before study drug administration
- The observation period is defined as the time of study drug administration to the last study visit

Treatment-emergent SAEs and AESIs are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the observation period.

Analysis

All SAEs and AESIs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The preferred term (PT), and the primary system organ class (SOC) will be listed.

Summaries by treatment group will include the following:

- The number (n) and percentage (%) of patients with at least 1 treatment-emergent serious adverse events (SAEs) through day 29 by system organ class and PT
- The number (n) and percentage (%) of patients with at least 1 infusion-related reactions (grade ≥2), through day 4 by PT
- The number (n) and percentage (%) of patients with at least 1 hypersensitivity reactions (grade ≥2), through day 29 by PT

Summaries of SAEs and AESIs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 event by SOC and PT
- SAEs and AESIs by severity (according to the grading scale outlined in Section 4.6.1), presented by SOC and PT
- SAEs and AESIs by relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent SAEs and AESIs
- The number (n) and percentage (%) of patients with Grade 3 or Grade 4 treatment-emergent adverse events (cohort 2 and cohort 3 <18 years only).

Deaths and other SAEs will also be listed and summarized by treatment arm.

5.8.2. Clinical Laboratory Measurements

Laboratory measurements include clinical chemistry and hematology results, and will be converted to standard international units and US conventional units. Summaries of laboratory variables based on standard international units will include:

- Descriptive statistics of laboratory result and change from baseline to Day 29. Summary statistics will include the number of patients, mean, median, standard deviation, quartiles, minimum, and maximum.
- Number and percentage of patients with a potentially clinically significant value (PCSV) at any post-randomization time point will be summarized for each clinical laboratory test for all patients and separately for patients in whom the PCSV criterion was normal or missing at baseline.
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest.

Listing of all laboratory parameters normal range and abnormal flag by patient and visit will be provided.

5.8.3. Analysis of Vital Signs

Vital signs (including temperature, blood pressure, pulse, and respiration) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics. The graphs of mean (or median) value of some vital sign parameter vs. visit will also be plotted.

5.9. Analysis of Pharmacokinetics, Pharmacodynamics and Biomarker Data

5.9.1. Analysis of Drug Concentration Data

Cohort 1 PK Sub-study
The concentrations of REGN10933 and REGN10987 in serum over time will be summarized descriptively for each of the treatment groups.

Cohort 2 Pediatric Patients
The concentrations of REGN10933 and REGN10987 in serum over time will be summarized descriptively by body weight tier and treatment group.

Cohort 3 Pregnant Women
The concentrations of REGN10933 and REGN10987 in serum over time will be summarized descriptively for each of the treatment groups.

5.9.2. Analysis of Pharmacokinetics and Pharmacokinetics/Pharmacodynamics

Exposure-response analyses for virologic, other select efficacy and safety endpoints, and/or biomarkers may be performed, as appropriate.

5.10. Analysis of Immunogenicity Data

5.10.1. Analysis of ADA Data

Immunogenicity variables will be summarized using descriptive statistics.

Immunogenicity will be characterized by the ADA responses and titers observed in subjects in the ADA analysis set.

ADA response categories and titer categories are defined as follows:

ADA response categories:

- ADA Negative, defined as ADA negative response in the ADA assay at all time points, regardless of any missing samples.
- Pre-existing immunoreactivity, defined as either an ADA positive response in the ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than 9-fold over baseline titer levels.
- Treatment-emergent response, defined as an ADA positive response in the ADA assay post first dose when baseline results are negative or missing. The treatment-emergent responses will be further characterized as Persistent, Indeterminate or Transient.
  - Persistent Response – Treatment-emergent ADA positive response with two or more consecutive ADA positive sampling time points, separated by at least 16-week period (based on nominal sampling time), with no ADA negative samples in between, regardless of any missing samples.
  - Indeterminate Response –Treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay, regardless of any missing samples.
  - Transient Response –Treatment-emergent ADA positive response that is not considered persistent or indeterminate, regardless of any missing samples.
- Treatment-boosted response, defined as a positive response in the ADA assay post first dose that is greater than or equal to 9-fold over baseline titer levels, when baseline results are positive

Titer categories (Maximum titer values)

- Low (titer <1,000)
- Moderate (1,000 ≤ titer ≤ 10,000)
- High (titer >10,000)

The following analysis will be provided:

- Number (n) and percent (%) of ADA-negative subjects (pre-existing immunoreactivity or negative in the ADA assays at all time points) by treatment arms

- Number (n) and percent (%) of treatment-emergent ADA positive subjects by treatment arms and ADA titer categories
  - Number (n) and percent (%) of persistent treatment-emergent ADA positive subjects
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive subjects
  - Number (n) and percent (%) of transient treatment-emergent ADA positive subjects
- Number (n) and percent (%) of treatment-boosted ADA positive subjects by treatment arms and ADA titer categories

Listing of all ADA titer levels will be provided for subjects with pre-existing, treatment-emergent and treatment-boosted ADA response.

5.10.2. Analysis of NAb Data

The absolute occurrence (n) and percent of subjects (%) with NAb status in the NAb analysis set will be provided by treatment groups.

5.11. Association of Immunogenicity with Exposure and Safety

5.11.1. Immunogenicity and Exposure

Potential association between immunogenicity variables and systemic exposure to REGN10933, and REGN10987 will be explored by treatment groups. Plots of drug concentration time profiles may be provided to examine the potential impact of ADA response status, and titer on these profiles.

5.11.2. Immunogenicity and Safety

Potential association between immunogenicity variables and safety may be explored with a primary focus on the following safety events during the TEAE period:

- Infusion reactions
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylaxis [Narrow]).

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Definitions of baseline for efficacy variables are defined in Section 4.5.

For safety variables, baseline will be the latest available valid measurement taken prior to the administration of study drug.

6.2. Data Handling Convention for Efficacy Variables

Not applicable.

6.3. Data Handling Convention for Missing Data

If pre-dose virologic results from the qualitative test are missing, then results from post-dose sample may be used to determine the qualitative PCR status at baseline, as long as the sample was collected 2 hours or less after starting study drug infusion.

For categorical variables, patients with missing data will be included in calculations of percentages. Number of patients with missing data will be presented.

Handling of Medications with missing/partial dates

To determine whether a medication is prior or concomitant medication, the missing medication start date is estimated as early as possible up to first dose date, and the missing medication end date is estimated as late as possible up to Day 29. If the medication start date is missing, the onset day will not be imputed in medication listings.

Handling of Adverse events Severity and Relatedness

If the intensity of a SAE, AESI and grade 3 or 4 AEs is missing, it will be classified as "Grade 3" in the frequency tables by CTC grade of SAE and AESIs. If the assessment of relationship of the investigational product is missing, it will be classified as related to the investigational product.

Date of infusions

Date of infusion is the non-missing administration date filled in the Study Drug Administration-IV CRF. If the first dose of study drug administration date is missing (even after site is queried), then the dosing date will be imputed with the randomization date. If any subsequent study drug administration date is missing, the date of dispensation of study drug from IRT will be used.

6.4. Visit Windows

Data analyzed by-visit-analysis will be summarized by the study scheduled visits described in Appendix 10.1, "Schedule of Event". The analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits, early termination visit (ETV) and end of treatment (EOT)/end of study (EOS) have the potential to be summarized. No analysis visit windows will be applied for the study scheduled visits nor for drug concentration/immunogenicity data.

The following analysis visit windows will be used to map the unscheduled visits, ETV and EOT visits for NP Swab for SARS-CoV-2 RT-qPCR, based on the study day during the double blind period:

Table 6: Time Window for Summary of NP Swab for SARS-CoV-2 RT-qPCR (Cohort 1 Patients; Cohort 3 Patients ≥ 18 Years)

Visit Label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	≤ 1
Day 7	7	[2, 10]
Day 15	15	[11, 22]
Day 29	29	[23, 32]

Table 7: Time Window for Summary of NP Swab for SARS-CoV-2 RT-qPCR (Cohort 2 Patients; Cohort 3 Patients < 18 Years)

Visit Label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	≤ 1
Day 3	3	[2, 4]
Day 7	7	[5, 10]
Day 15	15	[11, 22]
Day 29	29	[23, 32]

The following analysis visit windows will be used to map the unscheduled visits, ETV and EOT visits for laboratory and biomarker variables based on the study day during the double blind period:

Table 8: Time Window for Summary of Laboratory and Biomarker Variables except Serum for Serology (Cohort 1 Patients; Cohort 3 Patients ≥ 18 Years)

Visit Label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	≤ 1
Day 7	7	[2, 11]
Day 15	15	[12, 22]
Day 29	29	[23, 32]

Table 9: Time Window for Summary of Laboratory and Biomarker Variables except Serum for Serology (Cohort 2 Patients and Cohort 3 Patients <18 Years with Body Weight ≥ 10 kg)

Visit Label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	≤ 1
Day 7	7	[2, 11]
Day 15	15	[12, 22]
Day 29	29	[23, 32]

Table 10: Time Window for Summary of Serum for Serology (Cohort 1 Patients; Cohort 3 Patients ≥ 18 Years; Cohort 2 patients and Cohort 3 Patients <18 Years with Body Weight ≥ 10 kg)

Visit Label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	≤ 1
Day 29	29	[2, 32]

Table 11: Time Window for Summary of Laboratory and Biomarker Variables (Cohort 2 Patients with Body Weight < 10 kg)

Visit Label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	≤ 1
Day 7	7	[2, 18]
Day 29	29	[19, 32]

In the event of multiple measurements of the same test in the same window, if the measurements are from different categories, the priority order is scheduled, early termination visit then unscheduled visit. For the measurements in the same category, the value measured nearest to the target day will be assigned to the window; if they are at the same distance to the target day, the latest one will be used. Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing adverse events) will be included in listings, but not summaries except for the endpoint determination. If more than one laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

The determination of baselines and values at the end of treatment for both efficacy and safety variables will be based on scheduled available assessments and unscheduled available assessments.

6.5. Pooling of Centers for Statistical Analyses

Not applicable.

7. INTERIM ANALYSIS

Cohort 1

The final analysis of the primary efficacy endpoint, i.e., proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 for the 2400 mg group versus placebo comparison will be performed based on patients randomized on or before 17 January 2021. If the 2400 mg group versus placebo comparison is positive, an interim analysis of the primary endpoint for the 1200 mg group versus placebo comparison will be performed at α level of 0.01 based on patients randomized on or before 17 January 2021. If the interim analysis is positive for the 1200 mg group versus placebo comparison, this analysis will be considered as the final analysis and final analysis of the other key secondary analyses will be performed based on patients randomized on or before 17 January 2021. If the interim analysis is negative for the 1200 mg group versus placebo comparison, no further tests will be conducted for other key secondary endpoints at the interim analysis, and final analysis of the primary endpoint for the 1200 mg group versus placebo comparison and other key secondary analyses will be performed based on patients randomized on or before 24 February 2021.

The Gamma family alpha spending function (Hwang, Shih, DeCani 1990) based on the primary endpoint of proportion of patients with ≥1 COVID-19-related hospitalization or all-cause death through day 29 for the 1200 mg versus placebo comparison will be used to control for type I error for the planned interim analysis and the final analysis. The parameter for the Gamma family spending function will be calculated based on the information fraction of the interim analysis such that the alpha level at the interim analysis is equal to 0.01. If the interim analysis is not significant at 0.01 level for an endpoint, the remaining alpha level will be calculated based on the gamma parameter and information fraction. The information fraction will be determined based on the sample size in the mFAS at the interim analysis and final analysis of the primary endpoint for the 1200 mg group versus placebo comparison as follows: number of patients randomized to 1200 mg or placebo on or before 17 January 2021 in the mFAS divided by number of patients randomized to 1200 mg or placebo on or before 24 February 2021 (i.e., the day before the placebo treatment group was dropped per IDMC recommendation) in the mFAS.

Cohort 2 and 3

An interim descriptive analysis of phase 3 cohort 2 and 3 may be conducted for regulatory purposes when the phase 3 cohort 1 primary analysis is performed.

8. SOFTWARE

All analyses will be done using SAS Version 9.4.

9. REFERENCES

1. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med 2020; 382(19):1787-99.
2. Coronavirus Disease 2019 (COVID-19) Situation Report – 90. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/. Published 2020a. [Accessed] 20 April 2020.
3. ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
4. Hwang IK, Shih WJ, and DeCani JS. Group sequential designs using a family of type 1 error probability spending functions. Statistics in Medicine, 9:1439–1445, 1990.
5. Kim DH, Uno H, Wei LJ. Restricted mean survival time as a measure to interpret clinical trial results. JAMA cardiology. 2017 Nov 1;2(11):1179-80.
6. World Health Organization (WHO). Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). World Health Organization. https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf. Published 2020b. [Accessed] 10 March 2020.
7. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. Jama 2020b.
8. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020; 382(8):727-33.
9. Altman DG, Bland JM. Measurement in medicine: the analysis of method comparison studies. The Statistician 32 (1983), 307-317. 2.
10. Lin Li. A concordance correlation coefficient to evaluate reproducibility. Biometrics 45 (1989), 255-268.

10. APPENDIX

10.1. Schedule of Time and Events

Schedule of Events: Phase 3 (Cohort 1 Patients; Cohort 3 Patients ≥18 Years)

Day	Screening/Baseline Visit[1]				Follow Up[3]										EOS[3]
	-1 to 1				2	3	4	7	15	22	29	60	90	120	169
	Screen	Pre-Dose	Dose	Post-Dose											
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12
Window (Days)								±1	±3	±3	±3	±3	±3	±7[12,14]	±7[14]
Screening/Baseline Only															
Informed consent	X														
[redacted]	[redacted]														
[redacted]	X														
Inclusion/exclusion	X														
Antigen or molecular diagnostic test for SARS-CoV-2[5]	X														
Demographics	X														
Medical history (including COVID-19 illness, risk factors)	X														
Weight and height	X														
Randomization (treatment assignment)		X													
Treatment															
Study drug administration			X												
Efficacy															
Query for COVID-19-related medically-attended visit details								X	X	X	X				
NP swab for SARS-CoV-2 RT-qPCR		X						X	X		X				
Safety															
Vital signs		X[6]		X[6]											
Treatment-emergent grade ≥2 IRRs[7,8]			X	X	← cont. mon. →										
TEAEs that led to ***any*** medically-attended visit[7,8]				X	← continuous monitoring →										
Treatment-emergent grade ≥2 hypersensitivity[7,8]			X	X	← continuous monitoring →										
Treatment-emergent SAEs[7,8,16]			X	X	← continuous monitoring →										
Targeted concomitant medications[7, 8]	X		X	X	← continuous monitoring →										
Concomitant procedures[7,8]	X		X	X	← continuous monitoring →										

Day	Screening/Baseline Visit[1]				Follow Up[3]										EOS[3]
	-1 to 1				2	3	4	7	15	22	29	60	90	120	169
	Screen	Pre-Dose	Dose	Post-Dose											
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12
Window (Days)								±1	±3	±3	±3	±3	±3	±7[12,14]	±7[14]
Vital status[16]														X	X
Pregnancy test (women of childbearing potential)[9]	X														
Pregnancy status[16]														X	X
Safety information (newborns of study participants)[16]														X	X
Central Laboratory Safety Testing															
Hematology (including differential)	X[10]							X	X		X				
Blood chemistry (including AST, ALT, CRP, LDH)	X[10]							X	X		X				
Coagulation tests (D-dimer, PT/INR, aPTT)	X[10]							X	X		X				
Central Laboratory Immunogenicity Testing (Not Enrolled in PK Sub-Study, Not Pregnant at Randomization)															
Serum for ADA[13]	X[13]										X				
Central Laboratory Drug Concentration and Immunogenicity Testing (Enrolled in PK Sub-Study, Not Pregnant at Randomization)															
Serum for drug concentration (PK)[12]	X[10,12]										X[12]			X[12]	
Serum for ADA[13]	X[13]										X[13]			X[13]	
Central Laboratory Drug Concentration and Immunogenicity Testing (Pregnant at Randomization)															
Serum for drug concentration (PK)[12]	X[10,12]		X[12]								X[12]			X[12]	
Serum for ADA[13]	X[13]										X[13]			X[13]	
Central Laboratory Biomarker Testing															
Serum for serology	X[10]										X				
Serum for research	X[10]							X	X		X				
Plasma for research	X[10]							X	X		X				
Exploratory Patient-reported Outcomes															
SE-C19[14]		X			Daily										
PGIS[14]		X			Daily										
PGIC[14]											X				
Item: return to usual health		X			Daily										
Item: return to usual activities		X			Daily										
EQ-5D-5L[14]		X			Daily							X[14]	X[14]	X[14]	X[14]
WPAI+CIQ								X	X	X	X				
[redacted]															
[redacted]		X									X				

Day	Screening/Baseline Visit[1]				Follow Up[3]										EOS[3]
	-1 to 1				2	3	4	7	15	22	29	60	90	120	169
	Screen	Pre-Dose	Dose	Post-Dose											
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12
Window (Days)								±1	±3	±3	±3	±3	±3	±7[12,14]	±7[14]
[redacted]															
[redacted]		[redacted]													
[redacted]		[redacted]													

ADA, anti-drug antibodies; AE; adverse event; ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; CRP, c-reactive protein; EOS, end of study; INR, international normalized ratio; IRR, infusion-related reaction; LDH, lactate dehydrogenase; NP, nasopharyngeal; PBMC, peripheral blood mononuclear cells; [redacted]; PK, pharmacokinetics; PT, prothrombin time; SAE, serious adverse event; RT-qPCR, quantitative reverse transcription polymerase chain reaction; TEAE, treatment-emergent adverse event.

Schedule of Events: Phase 3 (Cohort 2 Patients; Cohort 3 Patients <18 Years)

Day	Screening/Baseline Visit[1]				Follow Up[3]										EOS[3]
	-1 to 1				2	3	4	7	15	22	29	60	90	120	169
	Screen	Pre-Dose	Dose	Post-Dose											
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12
Window (Days)								±1	±3	±3	±3	±3	±3	±7[14]	±7[14]
Screening/Baseline Only															
Parental informed consent and informed assent	X														
Inclusion/exclusion	X														
Antigen or molecular diagnostic test for SARS-CoV-2[5]	X														
Demographics	X														
Medical history (including COVID-19 illness, risk factors)	X														
Weight and height	X														
Randomization (treatment assignment)		X													
Randomization (PK-ADA schedule assignment)[15]		X													
Treatment															
Study drug administration			X												
Efficacy															
Query for COVID-19-related medically-attended visit details		X						X	X	X	X				
NP swab for SARS-CoV-2 RT-qPCR		X				X		X	X		X				
Safety															
Vital signs (≥12 years)		X[6]		X[6]											
Vital signs (<12 years)		X[6]	X[6]	X[6]											
Treatment-emergent grade ≥2 IRRs[7, 8]			X	X[17]	← cont. mon. →										
TEAEs that led to ***any*** medically-attended visit[7, 8]				X[17]	← continuous monitoring →										
Treatment-emergent grade ≥2 hypersensitivity[7, 8]			X	X[17]	← continuous monitoring →										
Treatment-emergent grade 3 or 4 AEs[8]			X	X[17]	← continuous monitoring →										
Treatment-emergent SAEs[7, 8,16]			X	X[17]	`← continuous monitoring →										
Targeted concomitant medications[7,8]	X		X	X[17]	← continuous monitoring →										
Concomitant procedures[7,8]	X		X	X[17]	← continuous monitoring →										
Vital status[16]														X	X
Pregnancy test (women of childbearing potential)[9]	X														
Pregnancy status[16]														X	X

Day	Screening/Baseline Visit[1]				Follow Up[3]										EOS[3]
	-1 to 1				2	3	4	7	15	22	29	60	90	120	169
	Screen	Pre-Dose	Dose	Post-Dose											
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12
Window (Days)								±1	±3	±3	±3	±3	±3	±7[14]	±7[14]
Safety information (newborns of study participants)[16]														X	X
Central Laboratory Safety Testing and Central Laboratory Biomarker Testing, Body Weight ≥20 kg															
Hematology (including differential)	X[10]							X	X		X				
Blood chemistry (including AST, ALT, CRP, LDH)	X[10]							X	X		X				
Serum for serology	X[10]										X				
Serum for exploratory research	X[10]							X	X		X				
Plasma for exploratory research	X[10]							X	X		X				
Central Laboratory Safety Testing and Central Laboratory Biomarker Testing, Body Weight ≥10 kg to <20 kg															
Hematology (including differential)	X[10]							X	X		X				
Blood chemistry (including AST, ALT, CRP, LDH)	X[10]							X	X		X				
Serum for serology	X[10]										X				
Central Laboratory Safety Testing and Central Laboratory Biomarker Testing, Body Weight <10 kg															
Hematology (including differential)	X[10]							X			X				
Blood chemistry (including AST, ALT, CRP, LDH)	X[10]							X			X				
Serum for serology	X[10]														
Central Laboratory Drug Concentration and Immunogenicity Testing (All Body Weight Tiers)															
Serum for PK-ADA (Schedule A)[15]	X[10,12]		X[12]			X[12]					X[12]				
Serum for PK-ADA (Schedule B)[15]	X[10,12]		X[12]					X[12]			X[12]				
Serum for PK-ADA (Schedule C)[15]	X[10,12]		X[12]						X[12]		X[12]				
Serum for PK-ADA (Schedule D)[15]	X[10,12]		X[12]							X[12]	X[12]				
Exploratory Patient-reported Outcomes (Age ≥12 Years Only)[14]															
SE-C19[14]		X			Daily										
PGIS[14]		X			Daily										
PGIC[14]											X				
Item: return to usual health		X			Daily										
Item: return to usual activities		X			Daily										
EQ-5D-Y-5L[14]		X			Daily							X[14]	X[14]	X[14]	X[14]
WPAI+CIQ								X	X	X	X				

Day	Screening/Baseline Visit[1]				Follow Up[3]										EOS[3]
	-1 to 1				2	3	4	7	15	22	29	60	90	120	169
	Screen	Pre-Dose	Dose	Post-Dose											
Visit Number	1				2	3	4	5	6	7	8	9	10	11	12
Window (Days)								±1	±3	±3	±3	±3	±3	±7[14]	±7[14]

ADA, anti-drug antibodies; AE; adverse event; ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; CRP, c-reactive protein; EOS, end of study; INR, international normalized ratio; IRR, infusion-related reaction; LDH, lactate dehydrogenase; NP, nasopharyngeal; [redacted]; PK, pharmacokinetics; PT, prothrombin time; SAE, serious adverse event; RT-qPCR, quantitative reverse transcription polymerase chain reaction; TEAE, treatment-emergent adverse event.

1. Screening visit may occur on the same day as, or the day prior to, the baseline visit.
2. [Phase 1 footnote removed]
3. On visit days where in-person sample collections or assessments are not required, information may be collected by phone.

[redacted]

5. Refer to Section 9.2.1.2 for diagnostic test requirements during screening.
6. Vital signs, including temperature, blood pressure, heart rate, and SpO_2 will be collected as described in Section 9.2.4.1.

   For **patients in cohort 1 and patients ≥12 years in cohort 2 and cohort 3**, vital signs will be taken once before the infusion and once after the infusion is completed. After infusion of study drug, these patients will be observed for at least 1 hour.

   For patients in **patients <12 years in cohort 2 and cohort 3**, vital signs will be taken before infusion, approximately every 30 minutes during the infusion, after the infusion is completed, approximately 1 hour post-infusion, and approximately 2 hours post-infusion. After infusion of study drug, these patients will be observed for at least 2 hours.
7. Treatment-emergent AESIs (grade ≥2 IRRs, grade ≥2 hypersensitivity, and TEAEs associated with ***any*** medically-attended visit) and treatment-emergent SAEs will be recorded until day 29. From day 30 to day 169, only treatment-emergent SAEs will be recorded. **For patients in cohort 2 and patients <18 years in cohort 3**, treatment-emergent grade 3 or 4 AEs will also be recorded until day 29. Refer to Section 10 for more information on reporting and recording requirements.

Targeted concomitant medications and concomitant procedures will also be reviewed and recorded. Refer to Section 9.2.4.3 for more information.

8. Continuously-monitored events will be recorded when they occur during the corresponding time period marked on the schedule of events. Study visits (including phone calls) are not required solely to collect continuously-monitored assessments, if no other assessments are planned on that day.
9. Pregnancy testing will be performed in women of childbearing potential (WOCBP) only and regardless of pregnancy status. A negative test is **not required** prior to study drug administration. Serum or urine pregnancy test are both acceptable. Refer to Section 9.2.6 for more information, including a definition of WOCBP.

   Note that a paper pregnancy report form must be completed for each patient who becomes pregnant or is pregnant at the signing of consent.
10. The indicated blood samples may be collected at the either day -1 or day 1 (ie, screening or pre-dose), but must be collected prior to randomization. For patients in phase 3 cohort 2, efforts should be made to collect all screening/pre-dose blood samples on the same study visit, when feasible.
11. [Footnote removed]
12. Actual dosing time and drug concentration sample collection times, as applicable, will be recorded.

    At the screening/baseline visit, blood for assessment of drug concentration in serum will be taken prior to dosing and within 60 minutes after the end of infusion (EOI). The EOI sample should be collected from the arm contralateral to that used for IV infusion. If not medically feasible, the EOI sample can be drawn from the same arm, but not from the infusion catheter.

    In cohort 1 and cohort 3 (≥18 years old), patients will follow different blood sample collection schedules for drug concentration and immunogenicity depending on whether they enrolled in the PK sub-study (cohort 1), not enrolled in the PK sub-study (cohort 1), or are pregnant at randomization (cohort 3 patients ≥18 years old). For samples collected on day 120, the collection window is ±28 days. Refer to Section 9.2.8 for more information on the PK sub-study.
13. The window for predose ADA sample collection is as close to administration of study drug as is reasonable. Actual dosing time and ADA sample collection times, as applicable, will be recorded.
14. **Patients in cohort 1 and patients ≥12 years in cohort 2 and cohort 3** will self-report symptoms using electronic surveys. The order of completion is as follows: SE-C19, PGIS, PGIC, return to usual health, return to usual activities, EQ-5D-5L, WPAI+CIQ. On days when a survey/questionnaire is not required it will be skipped, but the overall order will remain the same. Note that the WPAI+CIQ, EQ-5D-5L, and EQ-5D-Y-5L will only be administered at sites when regionally available.

On days 60, 90, 120, and 169, the window for electronic survey/questionnaire assessment is ±3 days. Note that study visits are not required on days when only electronic survey data are collected.

15. In **cohort 2 (and patients <18 years in cohort 3)**, each patient will be assigned at randomization by IWRS to a blood sample collection schedule for drug concentration and immunogenicity analysis. Actual dosing time and PK-ADA sample collection times will be recorded. To conserve blood volume, a single blood draw for drug concentration and immunogenicity will be obtained.
16. Patients will be followed by phone at day 120 and day 169 for vital status, pregnancy status, targeted safety information, and additional safety information in newborns of study participants. Refer to Section 9.2.5 for more information on these follow-up assessments.
17. **For patients <12 years in cohort 2 and cohort 3**, follow-up by phone will be conducted within 6 to 8 hours of infusion to collect the information indicated.

10.2. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	PCSV	Comments
Clinical Chemistry		
ALT*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required; multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
AST*	>3 and ≤ 5 ULN and baseline ≤ 3 ULN* >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007.

Parameter	PCSV	Comments
Total Bilirubin*	>1.5 and ≤ 2 ULN and baseline ≤ 1.5 ULN* >2 ULN and baseline ≤ 2.0 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤1.5, >1.5 to ≤2.0 and > 2.0 category for baseline vs. post baseline may be provided
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN, and baseline Total Bilirubin ≤ 35% or TBILI ≤1.5 ULN	Conjugated bilirubin determined on a case-by-case basis.
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN, and baseline ALT ≤ 3 ULN or TBILI ≤ 2ULN	Concept paper on DILI – FDA draft Guidance Oct 2007.
CPK*	>3 and ≤ 10 ULN and baseline ≤ 3ULN* >10 ULN and baseline ≤10ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤3, >3 to ≤10, and > 10 category for baseline vs. post baseline may be provided
Creatinine	≥150 µmol/L (Adults) or ≥ULN (if ULN≥150 µmol/L) and baseline < 150 µmol/L or <ULN (if ULN≥150 µmol/L) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994. 3 independent criteria

Parameter	PCSV	Comments
Creatinine Clearance (Cockcroft's formula)	<15 ml/min and baseline ≥15 ml/min (end stage renal impairment) ≥15 -<30 ml/min and baseline ≥30 ml/min (severe renal impairment) ≥30 - < 60 ml/min and baseline ≥60 ml/min (moderate renal impairment) ≥60 - < 90 ml/min and baseline ≥90 ml/min (mild renal impairment)	Use is optional. FDA draft guidance 2010 Four independent criteria, will provide additional shift table if needed
Uric Acid Hyperuricemia: Hypouricemia:	 >408 µmol/L or >ULN (if ULN≥408 µmol/L) and baseline ≤408 µmol/L or ≤ULN (if ULN≥408 µmol/L) <120 µmol/L or <LLN (if LLN≤120 µmol/L) and baseline ≥ 120 µmol/L or ≥LLN (if LLN≤120 µmol/L)	Harrison- Principles of Internal Medicine 17th Ed., 2008. Two independent criteria
Blood Urea Nitrogen	≥17 mmol/L or ≥ULN (if ULN≥17 mmol/L) and baseline <17 mmol/L or <ULN (if ULN≥17 mmol/L)	Two independent criteria
Chloride Hypochloremia: Hyperchloremia:	 <80 mmol/L or <LLN (if LLN≤80 mmol/L) and baseline ≥ 80 mmol/L or ≥LLN (if LLN≤80 mmol/L) >115 mmol/L or >ULN (if ULN≥115 mmol/L) and baseline ≤ 115 mmol/L or ≤ULN (if ULN≥115 mmol/L)	Two independent criteria
Sodium Hyponatremia: Hypernatremia:	 ≤129 mmol/L or ≤LLN (if LLN≤129 mmol/L) and baseline > 129 mmol/L or >LLN (if LLN≤129 mmol/L) ≥160 mmol/L or ≥ULN (if ULN≥160 mmol/L) and baseline <160 mmol/L or <ULN (if ULN≥160 mmol/L)	Two independent criteria

Parameter	PCSV	Comments
Potassium Hypokalemia Hyperkalemia	 <3 mmol/L or <LLN (if LLN≤3 mmol/L) and baseline ≥ 3 mmol/L or ≥LLN (if LLN≤3 mmol/L) ≥5.5 mmol/L or ≥ULN (if ULN≥5.5 mmol/L) and baseline <5.5 mmol/L or <ULN (if ULN≥5.5 mmol/L)	FDA Feb 2005. Two independent criteria
Total Cholesterol	≥7.74 mmol/L or ≥ULN (if ULN≥7.74 mmol/L) and baseline < 7.74 mmol/L or <ULN (if ULN≥7.74 mmol/L)	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L or ≥ULN (if ULN≥4.6 mmol/L) and baseline < 4.6 mmol/L or <ULN (if ULN≥4.6 mmol/L)	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN and baseline < 3 ULN	
Amylasemia	≥3 ULN and baseline < 3 ULN	
Glucose Hypoglycaemia Hyperglycaemia	 ≤3.9 mmol/L and <LLN and baseline >3.9 mmol/L or ≥ LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and baseline < 11.1 mmol/L (unfasted); <7 mmol/L (fasted)	 ADA Jan 2008.
HbA1c	>8% and baseline ≤ 8%	
Albumin	≤25 g/L or ≤LLN (if LLN≤25 g/L) and baseline >25 g/L or >LLN (if LLN≤25 g/L)	
CRP	>2 ULN or >10 mg/L (if ULN not provided) and baseline ≤2 ULN or ≤10 mg/L (if ULN not provided)	FDA Sept 2005.

Parameter	PCSV	Comments
Hematology		
WBC	<3.0 Giga/L or <LLN (if LLN≤3.0 Giga/L) and baseline ≥3.0 Giga/L or ≥LLN (if LLN≤3.0 Giga/L) (Non-Black); <2.0 Giga/L or <LLN (if LLN≤2.0 Giga/L) and baseline ≥2.0 Giga/L or ≥LLN (if LLN≤2.0 Giga/L) (Black)* ≥16.0 Giga/L or ≥ULN (if ULN≥16.0 Giga/L) and baseline < 16 Giga/L or <ULN (if ULN≥16.0 Giga/L)	Increase in WBC: not relevant. *The default criteria. Summary by race (black and Non-black) are optional. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L or >ULN (if ULN≥4.0 Giga/L) and baseline ≤ 4.0 Giga/L or ≤ULN (if ULN≥4.0 Giga/L)	
Neutrophils	<1.5 Giga/L or <LLN (if LLN≤1.5 Giga/L) for Non-Black or <1.0 Giga/L or <LLN (if LLN≤1.0 Giga/L) for Black and baseline ≥1.5 Giga/L or ≥LLN (if LLN≤1.5 Giga/L) for Non-Black or ≥1.0 Giga/L or ≥LLN (if LLN≤1.0 Giga/L) for Black* <1.5 Giga/L or <LLN (if LLN≤1.5 Giga/L) and baseline ≥1.5 Giga/L or ≥LLN (if LLN≤1.5 Giga/L) (Non-Black); <1.0 Giga/L or <LLN (if LLN≤1.0 Giga/L) and baseline ≥1.0 Giga/L or ≥LLN (if LLN≤1.0 Giga/L) (Black) <0.5 Giga/L regardless of baseline value or racce	International Consensus meeting on drug-induced blood cytopenias, 1991. *The default criteria. By race (black and Non-black) are optional.
Monocytes	>0.7 Giga/L or >ULN (if ULN≥0.7 Giga/L) and baseline ≤ 0.7 Giga/L or ≤ULN (if ULN≥0.7 Giga/L)	
Basophils	>0.1 Giga/L or >ULN (if ULN≥0.1 Giga/L) and baseline ≤ 0.1 Giga/L or ≤ULN (if ULN≥0.1 Giga/L)	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L) and baseline ≤0.5 Giga/L or ≤ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of Internal Medicine 17th Ed., 2008.

Parameter	PCSV	Comments
Hemoglobin	≤115 g/L or ≤LLN (if LLN≤115 g/L) for male or ≤95 g/L or ≤LLN (if LLN≤95 g/L) for female and baseline > 115 g/L or >LLN (if LLN≤115 g/L) for male or > 95 g/L or >LLN (if LLN≤95 g/L) for Female* ≤115 g/L or ≤LLN (if LLN≤115 g/L) and baseline > 115 g/L or >LLN (if LLN≤115 g/L) for male; ≤95 g/L or ≤LLN (if LLN≤95 g/L) and baseline > 95 g/L or >LLN (if LLN≤95 g/L) for Female. ≥185 g/L or ≥ULN (if ULN≥185 g/L) for male or ≥165 g/L or ≥ULN (if ULN≥165 g/L) for female and baseline <185 g/L or <ULN (if ULN≥185 g/L) for male or <165 g/L or <ULN (if ULN≥165 g/L) for Female* ≥185 g/L or ≥ULN (if ULN≥185 g/L) and baseline <185 g/L or <ULN (if ULN≥185 g/L) for Male; ≥165 g/L or ≥ULN (if ULN≥165 g/L) and baseline < 165 g/L or <ULN (if ULN≥165 g/L) for Female Decrease from Baseline ≥20 g/L	Three criteria are independent. *The default criteria. By gender (male and female) are optional. Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).

Parameter	PCSV	Comments
Hematocrit	≤0.37 v/v or ≤LLN (if LLN≤0.37 v/v) for Male or ≤0.32 v/v or ≤LLN (if LLN≤0.32 v/v) for Female and baseline > 0.37 v/v or >LLN (if LLN≤0.37 v/v) for Male or > 0.32 v/v or >LLN (if LLN≤0.32 v/v) for Female* ≤0.37 v/v or ≤LLN (if LLN≤0.37 v/v) and baseline > 0.37 v/v or >LLN (if LLN≤0.37 v/v) for Male ; ≤0.32 v/v or ≤LLN (if LLN≤0.32 v/v) and baseline > 0.32 v/v or >LLN (if LLN≤0.32v/v) for Female ≥0.55 v/v or ≥ULN (if ULN≥0.55 v/v) for Male or ≥0.5 v/v or ≥ULN (if ULN≥0.5 v/v) for Female and baseline < 0.55 v/v or <ULN (if ULN≥0.55 v/v) for Male < 0.5 v/v or <ULN (if ULN≥0.5 v/v) for Female* ≥0.55 v/v or ≥ULN (if ULN≥0.55 v/v) and baseline < 0.55 v/v or <ULN (if ULN≥0.55 v/v) for Male; ≥0.5 v/v or ≥ULN (if ULN≥0.5 v/v) and baseline < 0.5 v/v or <ULN (if ULN≥0.5 v/v) for Female	Two Criteria are independent *The default criteria. By gender (male and female) are optional.
RBC	≥6 Tera/L or ≥ULN (if ULN≥6 Tera/L) and baseline < 6 Tera/L or <ULN (if ULN≥6 Tera/L)	Unless specifically required for particular drug development, the analysis is redundant with that of Hb.
Platelets	<100 Giga/L or <LLN (if LLN≤100 Giga/L) and baseline ≥100 Giga/L or ≥LLN (if LLN≤100 Giga/L) ≥700 Giga/L or ≥ULN (if ULN≥700 Giga/L) and baseline < 700 Giga/L or <ULN (if ULN≥700 Giga/L)	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria

Parameter	PCSV	Comments
Urinalysis		
pH	≤4.6 or ≤LLN (if LLN≤4.6) and baseline > 4.6 or >LLN (if LLN≤4.6) ≥8 or ≥ULN (if ULN≥8) and baseline < 8 or <ULN (if ULN≥8)	Two independent criteria
Vital signs		
HR	<45 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions except STANDING
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions except STANDING
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions except STANDING
Weight	≥ 5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007

10.3. Symptom Evolution of COVID-19 (SE-C19)

Symptom Evolution of COVID-19 (SE-C19): The SE-C19 was developed based on the symptoms listed by the CDC, published literature and supported by interviews with patients with COVID-19. The symptom diary included a list of 23 symptoms (feverish, chills, sore throat, cough, shortness of breath or difficulty breathing, nausea, vomiting, diarrhea, headache, red or watery eyes, body aches, loss of taste or smell, fatigue, loss of appetite, confusion, dizziness, pressure or tight chest, chest pain, stomachache, rash, sneezing, sputum/phlegm, runny nose). On a daily basis, patients indicated which of the 23 symptoms they had experienced in the last 24 hours, and then rated each symptom selected at its worst moment in the last 24 hours on a scale of mild, moderate or severe. Each symptom on the SE-C19 was captured numerically as 0 (no symptom), 1 (mild symptom), 2 (moderate symptom), or 3 (severe symptom). For the purposes of analysis, 'no symptom' will be assigned a score of 0, 'mild symptom' and 'moderate symptom' will be assigned a score 1 (mild/moderate symptom), and 'severe symptom' will be assigned a score of 2 (ie, the mild and moderate symptom categories will be collapsed).

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